Electrical and Mechanical Insights of Human
Atrial Fibrillation

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Summary of PhD Thesis

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Introduction
Atrial fibrillation (AF) is the most common supraventricular arrhythmia in humans. Arrhythmogenic thoracic veins have been implicated not only in the initiation, but also in the perpetuation of atrial fibrillation. Pulmonary vein isolation is a mainstay technique of treatment of paroxysmal AF (PAF), however, ablation of persistent atrial fibrillation may require adjunctive methods of substrate modification. Both ablation targeting complex fractionated atrial electrograms (CFAE) recorded during AF and fractionated electrograms recorded during sinus rhythm (SRF) have been described but the relationship of CFAE to SRF is unclear.

Accurate mapping and representation of atrial rate throughout the atria during AF because sites of high atrial rate might represent structures critical to AF initiation and maintenance and amenable to ablation.

One possible way to achieve that is by measuring and averaging the cycle length (CL) of atrial activation at different sites across the atria in the time domain, however CFAEs frequently present a major obstacle to accurate CL measurement. Therefore another approach that is gaining popularity is to use spectral analysis of atrial electrograms which can be helpful when presenting spatial distribution of atrial rate in arrhythmias such as AF that show some irregularity in CL or signal amplitude.

Beyond the electrical considerations of AF, the potential mechanical consequences are also important and multiple factors contribute to functional mitral regurgitation (MR) in patients with AF. The relationship between AF associated left atrial (LA) remodeling, and its influence on the mitral apparatus have not been investigated.

Objectives
1. To elucidate the relationship between the distribution of CFAE/fragmented areas in the LA during AF and fragmented areas during SR, and analyse the mechanism of electrogram fractionation during SR.
2. To test our hypothesis that AF control after radiofrequency ablation (RFA) would result in reduction in MR by facilitating beneficial remodeling of the LA and mitral apparatus.
3. Using spectral analysis of AF, to investigate the distribution of dominant frequencies (DFs) in the atria and pulmonary veins (PVs) during PAF and the response to arrhythmogenic PV isolation.

Methods
1. Patients undergoing ablation of persistent AF were included in the study. Decapolar catheters were placed in the posterior right atrium (RA) and coronary sinus. A circular mapping catheter (10-pole, adjustable 15–25-mm Lasso, 6-mm bipole spacing, Biosense Webster, Diamond Bar, CA, USA) and a 3.5-mm tip irrigated ablation catheter (Celcius Thermocool, Biosense Webster; Diamond Bar CA) were introduced in the LA through double transseptal puncture.

CFAE maps
A three-dimensional LA geometry was created using the NavX electroanatomic mapping system (NavX, St. Jude Medical, St. Paul, MN). After the geometry was created, a detailed bipolar LA CFAE map was acquired during AF using the circular mapping catheter. The CFAE map
was acquired on-line using automated NavX algorithm.

**Sinus Rhythm Fractionation Map**

After DC cardioversion to sinus rhythm followed by a 5-minute waiting period, a second detailed bipolar LA activation map was acquired in SR, using the same circular mapping catheter. Care was taken to assure an even distribution of points throughout the left atrial geometry. Sinus rhythm fractionation (SRF) was calculated manually for each electrogram by counting the number of deflections present in each electrogram and recording the total number of deflections as the peak-to-peak voltage. In this manner, a color-coded sinus rhythm “fractionation map” could be displayed. Normal conduction typically results in three deflections of the bipolar electrogram. In order to determine a cutoff for the number of deflections that was considered “abnormal,” we determined the 95th percentile of electrogram deflections from our nine patient normal controls, after excluding septal points which have both right and left atrial components. We found that 95% of bipolar electrograms showed ≤ 5 deflections in our healthy control population, therefore electrograms with more than five deflections were defined as abnormally fragmented.

A frequency domain measure of left atrial sinus rhythm bipolar electrogram fractionation was also used. The “FFT ratio” (Fast Fourier Transformation ratio, FFTr) of high (>100 Hz) to total (0-300 Hz) spectral power was automatically computed and displayed on the electroanatomic map using a customized version of the NavX software. We found that an FFT ratio cutoff of >20% identified areas of fractionated electrograms during sinus rhythm.

**Left Atrial Activation Maps During Sinus Rhythm and Coronary Sinus Pacing**

The high density sinus rhythm maps also allowed a detailed reconstruction of left atrial endocardial activation. Regions of SRF were outlined on the LA geometry and activation patterns in regions of SR fractionation were examined in order to determine the mechanisms of fractionation. We hypothesized that areas of sinus rhythm fractionation might be related to wavefront collision. Finally, we also altered the pattern of wavefront propagation by pacing from the distal coronary sinus and repeating a third detailed bipolar activation map during coronary sinus pacing. The overlap between regions of LA fractionation recorded during CS pacing and regions of wavefront collision during CS pacing was calculated.

**Control group**

In order to determine the distribution of SRF in normal controls, nine control subjects without structural heart disease or history of AF underwent detailed bipolar LA maps in SR (CARTO XP, Biosense Webster, Diamond Bar, CA). These patients had all undergone mapping and ablation of paroxysmal supraventricular tachycardia.

**Quantitative analysis**

The LA surface was divided into 9 segments: left pulmonary veins, right pulmonary veins, roof, septum, anterior wall, lateral wall, posterior
wall, left atrial appendage and mitral annulus (extending 1 cm from the mitral valve plane). Each AF CFAE region, each SR fractionation region and each CS pacing fractionated region was outlined. The percentage of each anatomic segment that was encompassed by each fractionated region was calculated for each map. The percent overlap between CFAE and SRF was counted as the area common to both CFAE and SRF divided by the total area of CFAE. CFAE and SRF data were also exported to SPSS to calculate a correlation coefficient between maps. The percent overlap between the fractionated areas on the manual and automated FFTr maps was calculated as the area common to both regions divided by the total area of SRF in each segment. The percentage of areas of wavefront collision that were within regions of fractionation (# collisions within fractionated area / total # collisions) was calculated for the sinus rhythm and CS pacing maps.

**Voltage analysis**

Since the voltage characteristics of normal human LA are not well defined, we measured the global and regional unipolar (UNI) and bipolar (BI) signal amplitudes in the control patients to determine the optimal voltage cutoff for the normal left atrium. These data served as a standard for comparing the regional distribution of low voltage areas in AF population and controls. Finally, we analyzed the voltage in regions of SRF in AF patients compared to healthy controls.

**Methods 2.**

We performed a retrospective cohort study to determine whether AF is associated with significant atrial functional MR. Reports from transthoracic echocardiograms performed within 3 days of catheter ablation of AF were screened, and an experienced research echocardiographer analyzed the images of those with greater than mild MR. All patients with secondary Type I MR of at least moderate severity and who also had complete 1-year clinical follow-up after ablation were included in the MR cohort. The reference cohort was randomly selected in a 1-to-1 fashion from those patients with mild or less MR on initial report screening and subsequent image analysis and who also had complete 1-year clinical follow-up. Patients with an ejection fraction <50% were excluded to avoid including patients whose MR might be due to ventricular dysfunction. Demographic and clinical information were prospectively obtained in all patients. The clinical AF syndrome was determined based on the predominant arrhythmia presentation at the time of admission and was defined as paroxysmal if AF episodes were self-terminating in <7 days and persistent if typical AF episodes lasted >7 days and/or required intervention for termination.

**Ablation procedure**

All patients underwent proximal antral PVI, guided by intracardiac echocardiogram and circular multipolar electrode catheter recordings and elimination of all proviable PV triggers and all non-PV triggers resulting in AF. All 4 PVs were isolated routinely in patients with a history of
persistent AF, those without provicable AF triggers, and those patients with significant risk factors for AF including a history of hypertension, LA enlargement, and those over the age of 50 years. In the remaining selected patients, we isolated arrhythmogenic PVs only.

Patient follow-up

Patients were clinically evaluated as outpatients at 6 to 12 weeks, 6 months, and 1 year, at which time they were queried for symptoms and 12-lead electrocardiograms were obtained. Echocardiograms were performed at the first visit and at the second or third visits, at the treating physician’s discretion. Antiarrhythmic medications were typically discontinued at 6 to 12 weeks if patients had paroxysmal AF and at 6 months if they had persistent AF, but were continued beyond this point in selected patients based on doctor and/or patient preference even in the absence of an arrhythmia event. The patients were provided with a transtelephonic monitor (TTM) and instructed to transmit 2 times daily and with symptoms during the first 4 weeks after ablation. They were then instructed to transmit once at 6 to 12 weeks, then once at 6 months and 1 year. Patients also made additional TTM transmission if they had any arrhythmia symptoms at any time during follow-up and/or when antiarrhythmic medications were discontinued. One-year AF recurrence was defined according to consensus guidelines as any documented electrocardiographic episode of atrial arrhythmia lasting 30 s or longer with or without symptoms. Recurrence at the time of follow-up echocardiography was defined as any electrocardiographic recurrence during the 6 months preceding the echocardiogram.

Echocardiography

Standard 2-dimensional and Doppler echocardiography with color flow mapping was performed according to the standard clinical protocol. Echocardiograms were then analyzed offline by a single research echocardiographer, blinded to patient outcomes and to the relative timing of the echocardiogram. LA anterior–posterior systolic diameter was measured in the parasternal long-axis view, and the major axis of the LA was measured in the apical 4-chamber view. LA area at end-systole was measured in the apical 2- and 4-chamber views. Similarly, LA volumes at end-systole were measured in the apical 2- and 4-chamber views using a single-plane modified Simpson’s method of discs, and values averaged. Mitral annular dimensions were measured in parasternal long-axis, apical 2-chamber, and apical long-axis views. MR color jet area was measured in the apical 4-chamber, apical 2-chamber, and apical long-axis views. Color Doppler scale and, therefore, Nyquist limit were determined by the clinical ultrasonographer and in general were set to 50 to 70 cm/s. The ratio of MR color jet area to LA area (MR/LA ratio) was then calculated, using the largest measured values for both. Mild MR was defined as a MR/LA ratio of ≥0.1 to ≤0.2, moderate MR as ≥0.2 to ≤0.4, and severe as ≥0.4. Only patients with moderate or greater MR were included in the MR
cohort. Leaflet motion was characterized as normal, excessive, or restrictive. Only patients with normal mitral leaflet motion (Carpentier Type I) were included in the MR cohort. Patients with any evidence of primary leaflet involvement, such as from prior endocarditis, rheumatic valve disease, congenital anomaly, or significant mitral annular calcification, were excluded.

Methods 3.

To test the spectral analysis of AF we aimed to characterize the dominant frequency (DF) distribution in the atria and PVs shortly after initiation and during sustained paroxysmal AF in relation to the specific arrhythmogenic structure triggering the episode. Test patients were included if they had frequent episodes of PAF resistant to at least one antiarrhythmic medication. Exclusion criteria were previous catheter ablation for PAF, non-paroxysmal AF, previous heart surgery involving atriotomy, severe valvular heart disease, LA thrombosis and/or contraindications to prolonged anticoagulation.

Electrophysiological study and follow-up

Following femoral venous access decapolar steerable electrophysiologic catheters (interelectrode spacing 2-5-2 mm, Dynamic Deca, Bard Electrophysiology, Lowell, MA, USA) were positioned in the CS and at the posterolateral RA wall with the distal bipole at the junction between the RA and superior vena cava (SVC). After double transseptal puncture a decapolar circular mapping catheter (Inquiry Optima, St. Jude Medical, Irvine, CA, USA) and a quadripolar, 3.5 mm irrigated tip mapping/ablation catheter (Navistar Thermocool, Biosense Webster, California, USA) were advanced to the LA. Intracardiac echocardiography (ICE) (AcuNav, Acuson Corp, Mountain View, CA, USA) was used to define the PV ostia and to guide catheter positioning. Initially, the circular mapping catheter was positioned at the left PV antrum and the mapping/ablation catheter was steered to the carina between the right PVs. If the patient presented to the EP lab in sinus rhythm PAF induction was attempted by isoproterenol infusion at a starting dose of 3 µg/min with subsequent increments of 5 µg/min until PAF was induced, the patient developed side effects or the maximum dose of 20 µg/min was reached.

If the presenting rhythm was AF transthoracic electrical cardioversion was performed before proceeding to AF induction. Atrial premature depolarizations (APDs) identified as PAF triggers were recorded using the above mentioned catheter configuration and the endocardial activation sequence was analyzed. Early activation at the poles positioned in the superior or inferior regions of the left antrum with LA-PV electrogram reversal was considered to signify left superior (LSPV) or left inferior pulmonary vein (LIPV) origin of the APDs, respectively. to determine their origin Triggers demonstrating early activation at the poles located at the level of the left carina were considered to arise from the left PVs without further specifying their origin to the LSPV or LIPV. APDs were considered to arise from the right PVs if the earliest activation during APD was
recorded at the right PV carina and the quadripolar catheter positioned there demonstrated distal to proximal activation and/or LA-PV potential reversal. When earliest atrial activation was recorded at any of the CS or RA bipoles these structures were identified as triggers. Upon induction of sustained AF isoproterenol infusion was discontinued and further signal recordings were made after a 5 min waiting period. During sustained AF the circular catheter was used to record signals sequentially from each PV ostium and the LA posterior wall (LAPW) simultaneously with recordings from the RA and CS. After achieving stable catheter position as assessed by fluoroscopy and ICE, signals were recorded for at least 30 sec from all catheter bipoles at a sampling rate of 997 Hz/sec using a commercially available digital EP recording system (GE Cardiolab, General Electrics, Milwaukee, WI, USA).

Signal analysis

Intracardiac signals were analysed utilizing a custom designed computer application prepared with the LabView software package (National Instruments, Austin, Texas). Signals were bandpass filtered between 30 and 500 Hz, rectified and then low-pass filtered at 20 Hz. Following this preprocessing a FFT with a Hanning window was performed on two consecutive 5-seconds episodes of the signal from each bipolar from all catheters (frequency resolution 0.2 Hz). The frequency spectrum in the 3-15 Hz range was obtained and the DF was determined as the peak with the highest power. Regularity index (RI) was also calculated as the ratio of the area under the DF peak and its harmonics to the area under the whole spectrum curve in the above mentioned frequency range. The maximum DF value from all bipoles of each structure was taken as the DF of that structure and used for further analysis.

Results 1

Twenty patients with persistent AF were included in the study.

Comparison of AF CFAE and SR Fractionation Maps

An average of 418 ± 135, and 338 ± 150 points were acquired for the CFAE and SRF maps, respectively. CFAE comprised 25 ±15% of the LA surface area. CFAE regions were most prevalent on the LA septum (37%), anterior wall (44%) the roof of LA (45%), and least prevalent in the LAA (14%). SR fractionation encompassed 29 ±14% of the left atrium. SR fractionation was most prevalent on the LA septum (53%) and anterior wall (45%), and least prevalent in the LAA (12%).

Despite the similar general distributions of the two different measures of electrogram fractionation, the location of the actual SRF and CFAE regions were typically different, with only 32±16% overlap. There was also no significant correlation between SR fractionation and CFAE maps (r=0.2 p=0.24).

On the other hand, the appearance of the manual SR fractionation and automated FFTr maps was quite similar, with abnormal electrograms using both techniques comprising 29±14 and 31±12 % of the LA surface area, respectively. There was a significant correlation between SRF, and FFTr...
maps (r=0.6 p<0.01) with 75% overlap between the SRF and FFTr maps.

SR Fractionation and Wavefront Collision

Analyzing the left atrial endocardial activation using the high density sinus rhythm maps, areas of wavefront collision were encompassed by regions of SRF 75±13% of the time. When activation maps were then repeated during coronary sinus pacing at 500ms, there was a shift in the areas of wavefront collision. Along with these shifts in areas of wavefront collision during CS pacing, there was a parallel shift in regions of electrogram fractionation such that there continued to be an 87±13% overlap between areas of fractionation during CS pacing and regions of wavefront collision. This suggests that the majority of the regions of sinus rhythm fractionation, whether recorded during sinus rhythm or CS pacing, were due to wavefront collision rather than some inherent characteristic of the local atrial tissue.

Control group

In 9 patients with structurally normal hearts, detailed SRF maps were acquired. In normal atria, SRF was most prevalent on the LA septum (65%) and anterior wall (49%), and least prevalent in the LA appendage (8%). SRF in patients with AF and controls comprised 29±14% and 32±20% of the LA surface area, respectively. There was no significant difference in the distribution of SRF between the 9 healthy control patients and the 20 patients with a history of AF (p=0.74)

Voltage characteristics

In control patients, the global mean LA BI and UNI voltage amplitude in SR were 2.83±2.25 mV and 4.12±2.14 mV, respectively; 95% of all BI and UNI electrograms recorded from the LA were >0.50 and >1.57 mV, respectively.

There was no difference in mean LA BI voltage between the AF patients and the controls (2.80 ± 2.75 mV vs 2.83 ± 2.25 mV; p=0.68). Using the 0.5 mV as a BI voltage cutoff indicating abnormal atrial substrate, we calculated the percentage of low voltage areas (<0.5 mV) in each LA segment (excluding the pulmonary veins) in AF patients and normal subjects. In healthy controls, low voltage signals were present rarely in the LA septum (1%), roof (2%), anterior wall (2%), posterior wall (3%), lateral wall (4%), mitral annulus (4%), and LA appendage (0%). There was no difference in the segmental distribution of low voltage areas between AF patients and healthy controls (p=0.829).

Results 2

There were 97 patients who met our criteria for significant MR after study review. Of these, 54 had normal leaflet motion with no apparent primary leaflet pathology (6.5% of all patients undergoing first ablation), 53 of whom had 1-year clinical follow-up and were included as the MR cohort. One patient required mitral valve surgery in the first year after ablation, but after her 6-month echocardiogram, and was included in the analyses. Of the
660 patients with mild or less MR and 1-year clinical follow-up, 53 patients were randomly selected as the reference cohort. Patients with MR were older, more likely to have persistent AF, and more frequently had hypertension. Ninety-seven percent of patients were in sinus rhythm at the time of their baseline echocardiogram. Patients with MR had significantly larger LA size by several measures and larger mitral annular dimensions, but no difference in any measure of left ventricular size or function. Among the reference cohort, 60% had trace or no MR and 40% had mild MR. In the MR cohort, 72% had moderate MR and 28% had severe MR. Binary logistic regression models were constructed to determine the variables that were independently associated with significant MR. Mitral annular dimension had the largest odds ratio in the final model (8.39 per cm, 95% CI: 1.94 to 36.35 per cm, p = 0.004).

Follow-up echocardiography

Follow-up echocardiograms were available in 32 of the 53 patients in the MR cohort, an average of 277 days after ablation. Rhythm status at follow-up was defined as described above, applied only to the 6 months preceding echocardiography. By this definition, 21 patients were free of recurrence and 11 patients had recurrence of AF. Ninety-four percent of patients were in sinus rhythm at the time of follow-up echocardiography. At the time of ablation, patients with eventual recurrence had larger measures of LA size (LA volume index: 41.3 cm³/m² vs. 28.2 cm³/m², p = 0.02), with nonsignificant trends towards larger regurgitant jet area and mitral annular dimension. Other echocardiographic measures were not significantly different between the 2 groups at baseline.

At follow-up, both groups had reductions in LA size, but only the group in sinus rhythm had a significant decrease in mitral annular dimension (3.41 cm at baseline to 3.24 cm at follow-up, p = 0.02). Both groups experienced some decrease in MR, but at follow-up, the patients in sinus rhythm had significantly less MR than patients with AF recurrence (MR/LA ratio: 0.16 vs. 0.28, p = 0.005) (Table 4), despite being similar at baseline. At baseline both groups had similar percentages of patients with moderate and severe MR (p = 0.72). At follow-up, 19% of the patients in sinus rhythm had trace or no MR, compared with 0% in the recurrence group, and 57% in the sinus rhythm group had mild MR compared with 18% in the recurrence group. Only 24% of the sinus rhythm patients still had significant MR at follow-up, compared with 82% in the recurrence group (p = 0.005 for entire trend).

Results 3

Isoproterenol infusion at a dose of 11.05 ± 4.76 µg/min led to induction of sustained AF in 26 patients (93%) that were further studied.
PAF was triggered by APDs from the PVs in 24 patients and from the SVC/RA junction in two. PV triggers were found to originate from the LSPV in 11 (42.3 %), from the LIPV in 2 (7.7 %), from the right PVs in 4 (15.4%). In 7 (26.9%) the trigger was localized to the carina region between LSPV and LIPV. The arrhythmogenic structures had the highest DF in 22 patients (84.6%). This includes the two patients with RA trigger in whom the highest DF was found in the RA. In the remaining patients a slightly higher DF was recorded from non-arrhythmogenic PVs. In the recording there was a significant difference in the DF among the arrhythmogenic structures, the PVs, the LAPW, the CS and the RA (8.07 ± 1.5 Hz vs. 6.65 ± 1.36 Hz vs. 6.06 ± 0.7 Hz vs. 6.01 ± 0.68 Hz vs. 5.93 ± 0.78 Hz, respectively, p < 0.0001). The pairwise analysis showed a significantly higher DF in the arrhythmogenic structures compared to the PVs (mean difference 1.42 ± 0.27 Hz, p < 0.0001), LAPW (mean difference 2.02 ± 0.32 Hz, p < 0.0001), CS (mean difference 2.07 ± 0.32 Hz, p < 0.0001), and RA (mean difference 2.15 ± 0.35 Hz, p < 0.0001). Among the 24 patients with PV triggers spontaneous termination occurred in 5 (21%) patients. Acute termination during ablation was observed in 14 (74%) of the remaining 19 patients. Nine of the 14 patients (64%) had AF termination upon isolating the arrhythmogenic PV antrum. The arrhythmia continued despite arrhythmogenic PV isolation in 10 of 19 patients (53%). Contralateral PV antrum isolation as a second step resulted in AF termination in 5 patients (26%). Another 5 patients were cardioverted after all PVs were isolated. One of them needed additional lesions for complete PV isolation.

Discussion

1. In our study of patients with persistent AF, we found that 1) there is little correlation between the location of CFAE recorded during AF and fractionated electrograms recorded during sinus rhythm 2) fractionated electrograms recorded during sinus rhythm are mainly caused by wavefront collision in the LA and 3) the presence and distribution of sinus rhythm fractionation in patients with a history of AF is the same as in control patients without a history of AF. Finally, we also found that a signal processing measure, the FFT ratio, closely approximated a manual measure of sinus rhythm fractionation. Together, these findings imply that fractionated electrograms recorded during sinus rhythm, whether measured in the time or frequency domain, are a normal finding in the human LA due to wavefront collision, and are not evidence of underlying tissue characteristics that serve to maintain AF.

2. The results of our retrospective cohort study demonstrated, that frequency of mild to moderate or more severe MR is more common in the unique population undergoing AF ablation comparing to historical controls.. Second, after a successful AF ablation procedure, the LA size and dimensions, mitral annular diameters and consequently, the degree of functional MR decreased significantly in a subset of AF patients presented
with mild to moderate or more severe MR at baseline in contrast with patients with failed procedure. We refer to this as atrial functional MR, and clinical characteristics associated with this MR were older age, hypertension, and most powerfully, persistent rather than paroxysmal AF. By echocardiography, MR was associated with increased LA size and mitral annular dilation. After multivariate regression, we found that only age, persistent AF, and mitral annular dilation were linked to MR. This suggests that LA size, notably not independently correlated with MR, may mediate its impact via its effect on the mitral annulus.

By studying follow-up echocardiograms after AF ablation, we were able to evaluate possible pathophysiological mechanisms underlying atrial functional MR. Patients with successful ablations experienced significant reductions in LA size and mitral annular dimension, and less than a third still had significant MR at follow-up. In contrast, among patients who had recurrence of AF, there was no significant change in annular dimension despite near-significant reductions in LA size. Over 80% of the patients with recurrence still had significant MR at follow-up. These findings, combined with those from our regression model, which showed that mitral annular dimension was the only independent echocardiographic predictor of MR, strongly suggest that atrial functional MR is mediated through a process of annular dilatation. Based upon this observation, it can be assumed that beyond the regression of dilated chambers, the potential recovery of the mechanical function can be beneficial on the active motion of mitral leaflets.

3. This study demonstrates that in most patients with PAF the arrhythmogenic structures show the highest DF peak during spectral analysis. Moreover, termination of PAF by ablation occurs most frequently during isolation of arrhythmogenic PVs. Due to wave breakdown and emergence of complex block pattern multiple, well-demarcated DF domains are formed in the atria as a hallmark of fibrillatory conduction. These domains are spatially distributed in a hierarchical order with the highest DF located in the LA and the lowest in the RA. Studies using frequency mapping during AF in both animal models and humans also support the role of PVs in AF maintenance showing the highest DF to be recorded at the PVs. The presence of a DF gradient from the LA to RA has been shown by Lazar et al. in patients with PAF but not in those with persistent AF. This gradient is abolished with PV isolation and has been found to recover in patients undergoing repeat procedures due to arrhythmia recurrence.

**Conclusion**

1. There is little overlap between regions of CFAE recorded during AF and regions of SR fractionation. During sinus rhythm, fractionated electrograms typically occur in regions of wavefront collision. There is no significant difference in the frequency and distribution of fractionated electrograms recorded during sinus rhythm in patients with and without AF. These
findings suggest SRF is not a surrogate for CFAE during AF ablation and SRF itself may not be a suitable ablation target.

2 Patients with AF and significant MR with AF control after RFA had significant reduction in LA dimensions, mitral annular size and MR. These observations suggest a potential relationship between atrial fibrillation and functional mitral regurgitation due to atrial enlargement and annular dilation, and these detrimental effects can be reversed with control of AF after RFA.

3 Frequency analysis is a feasible technique which can reliably identify the arrhythmogenic structures which should be the main targets of ablation therapy in PAF patients. Triggering structures show the highest activation rate during PAF, suggesting their major role not only in the initiation but also in the maintenance of human AF.

**LIST OF PUBLICATIONS RELATED TO THE THESIS**


