Spatial Changes in Refractoriness Over Time Following Cardioversion of Atrial Fibrillation Predicts Recurrence

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CERTIFICATE OF APPROVAL

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Acknowlegements

Thanks to Merritt Raitt M.D. who was my research supervisor

Definition of Terms

Effective refractory period (ERP): The average of the longest coupling interval between the basic drive train and the premature impulse which fails to propagate through the tissue.

Dispersion of refractoriness: The difference between the maximum and minimum ERP measured at various atrial sites for each drive train cycle length at a specific time point.

Change in dispersion: The absolute difference in dispersion of refractoriness between 10 minutes and at 1 hour.

Dispersion Instability: A change in dispersion of greater than 10 ms at paced cycle length 550 ms.

Atrial electrical remodeling: shortening of atrial refractoriness period and loss of physiological adaptation of atrial refractoriness to heart rate during atrial fibrillation.

Reverse atrial electrical remodeling: Lengthening of atrial refractoriness period and the return of normal adaptation of atrial refractoriness to heart rate with restoration of normal rhythm following a period of atrial fibrillation.

Reverse remodeling proportion: The proportion of atria at all measured sites and cycle lengths undergoing reverse remodeling (ERP increase of greater than 2 ms between 10 minutes and 1 hour following cardioversion).

Minimal reverse atrial electrical remodeling: Less than 25% of the measured sites and cycle lengths demonstrating a 2 millisecond increase in ERP over 1 hour (remodeling proportion <0.25).

Heterogeneous reverse atrial electrical remodeling: greater than or equal to 25% of the atria but less than or equal to 75% of the atria demonstrating a 2 millisecond increase in ERP over 1 hour (0.25<= remodeling proportion<=0.75).

Homogeneous reverse atrial electrical remodeling: Greater than 75% of the atria demonstrating a 2 millisecond increase in ERP over 1 hour (remodeling proportion >0.75).

Non-sustained atrial fibrillation: Atrial fibrillation not requiring cardioversion.

Sustained atrial fibrillation: Atrial fibrillation requiring cardioversion.

Abstract

Background: Atrial fibrillation (AF) recurrence following cardioversion may be due to dispersion of refractoriness and atrial electrical remodeling. Given the temporal changes in refractoriness following cardioversion, it is likely that dispersion of refractoriness following cardioversion is dynamic rather than a static process. If dispersion of refractoriness is dynamic,

time would be an important factor in studying the association between dispersion of refractoriness and recurrence of AF. Therefore I hypothesized that a greater change in dispersion of refractoriness, or dispersion instability following cardioversion may be associated with an increase in risk of atrial fibrillation recurrence.

Methods and Results: Forty patients (71.1±3.3 yrs, left atrial diameter 43±12 mm, lone AF 17.5%, free of class I and III anti-arrhythmics) with persistent (greater than 30 days but less than 1 year) atrial fibrillation were studied. Multipolar catheters were positioned along the lateral right atrial wall and the coronary sinus. Atrial effective refractory period was measured at three atrial sites (high right atrium, coronary sinus os, and distal coronary sinus) at two different time points after cardioversion. The changes in atrial refractoriness over time, differences in refractoriness between atrial sites (dispersion), and change in dispersion over time were studied in relationship to the recurrence of AF. Reverse atrial electrical remodeling at the right atrium was not a predictor of atrial fibrillation recurrence. The proportion of atria at all measured sites and cycle lengths undergoing reverse remodeling (ERP increase of greater than 2 ms between 10 minutes and 1 hour following cardioversion) were divided into upper 25% (homogeneous reverse atrial electrical remodeling), middle 50% (heterogeneous reverse atrial electrical remodeling) and lower 25% (minimal reverse atrial electrical remodeling). Patients who underwent either minimal reverse atrial remodeling or homogeneous reverse atrial electrical remodeling had a decreased risk of AF recurrence (1/8 patients with recurrence in both groups). However, patients who underwent heterogeneous reverse atrial electrical remodeling had an increased risk of AF recurrence (15/19 patients with AF recurrence, RR=22.5, p=0.003). Dispersion of refractoriness at a single time point was a poor predictor of AF recurrence. The change in dispersion of refractoriness over time was calculated as the absolute difference in dispersion between 10

minutes and 1 hour (Cl 550: 10.8 ms; Cl 400 ms: 10.1 ms). Patients with greater than the median (10 ms) change in dispersion at Cl 550 ms were at increased risk of AF recurrence (RR=9, p=0.007). These electrophysiological parameters were compared with clinical parameters in predicting the recurrence of AF. Logistic regression revealed that change in dispersion at drive train Cl 550 ms, heterogeneous reverse atrial electrical remodeling, and RA pressure >10 mm were associated with an increase risk of AF recurrence. Change in dispersion of >10 ms was the strongest predictor of time to recurrence of AF (RR=12.23, p=0.02) in a Cox regression.

Conclusion: Patients with persistent AF and greater change in dispersion, or dispersion instability, were at increased risk of AF recurrence following cardioversion.

Background

Atrial fibrillation (AF) is the most common arrhythmia affecting humans (1). With age, the prevalence of AF increases (up to 9% in octogenarians) (1). AF is associated with significant morbidity and mortality and places a significant financial burden on society (1). Morbidities associated with AF include an increased stroke risk (up to 30% of strokes over age 70), and impaired quality of life due to the symptoms associated with AF (1). Hundreds of millions of dollars are spent annually to treat this arrhythmia and its associated complications (1). Treatment of atrial fibrillation includes heart rate control, anticoagulation, and termination by cardioversion.

However cardioversion of AF is a clinically frustrating strategy due to the high recurrence risk. The risk of recurrence of AF following cardioversion is about 50% at 6 months with the vast majority of recurrences in the first 2 weeks (13). Successful maintenance of sinus rhythm after cardioversion of AF is thought to be dependent on factors such as duration of AF, age, left ventricular systolic function, and size of left atrium (14). However none of these factors have turned out to be consistently useful in predicting AF recurrence. The lack of a consistent clinical factor in predicting AF recurrence and the association of abnormal refractoriness of the atria with AF may suggest that electrophysiological properties are important determinants of atrial vulnerability to AF.

AF is electrophysiologically characterized by random waves of depolarization circulating in the atria which become more persistent with time (1,2). The most widely accepted theory on the mechanism of AF is based on the multiple wavelet hypothesis (3).

In Moes multiple wavelet theory, multiple reentrant impulses of different sizes wander through the atria, creating continuous atrial electrical activity (3). The wavelets are a leading circle type with a functional conduction block at the center, which prevents collapse and extinction of the wavelets (4). Since AF may require a critical number of wavelets, the wavelength is important for the perpetuation of AF (4). The wavelength is the product of conduction velocity and refractory period. The conduction velocity is the speed at which the wave of depolarization travels through the atrial tissue, while the refractory period is the phase where another wave of depolarization cannot activate the cell (5). If the wavelength is relatively long, fewer waves can circulate through the atria, and fibrillation will tend to self terminate (6). However, when the wavelength is short, a greater number of wavelets can be present, and fibrillation will be sustained (4). Another factor favoring the onset and maintenance is the spatial relationship of refractoriness in the atria, or dispersion of refractoriness (7). During the onset of AF, dispersion of refractoriness increases the chances of local unidirectional block (8). Unidirectional block in turn is a prerequisite for the initiation of a reentrant circuit and may be a precursor to AF (8). Once AF is initiated, wavelets propagate in a varying pattern around continuously shifting areas of functional conduction block in the atria (8). This shifting conduction block is due to non-uniform recovery of excitability within the atria and favors maintenance of AF.

AF may also be a self perpetuating process, where "AF begets AF" (9). Animal studies have suggested that abnormal refractoriness may explain the progression towards persistence of AF (9). In this study, AF was associated with a shortening of atrial refractoriness and loss of physiological adaptation of atrial refractoriness to heart rate (9).

These changes were termed atrial electrical remodeling (9). It has been further suggested that shortening in refractoriness favors AF by decreasing wavelength and results in a greater number of potential electrical reentrant wavelets in the atria as predicted by the multiple wavelet hypothesis (9). In animal models, the atrial electrical remodeling process is reversible and within 1 week following cardioversion of AF, atrial refractoriness returns to normal (10-12). During reverse atrial electrical remodeling, the atria are vulnerable to AF. This may explain the high AF recurrence risk in the early weeks following cardioversion.

In humans, AF has been characterized by short effective refractory period (9), and increased dispersion of refractoriness (8). However, there is limited and conflicting data as to the utility of these parameters to predict recurrence of AF following cardioversion. A small study of patients with AF and a short effective refractory period (ERP) following cardioversion were more likely to relapse (15). A more recent study found that patients with AF and a longer ERP following cardioversion were more likely to recur (16). Yet another study showed that dispersion of refractoriness utilizing the ERP as a measurement of refractoriness did not predict recurrence (17).

Researchers have suggested that completion of the reversal of atrial electrical remodeling (where the ERP returns to normal) following cardioversion decreases the likelihood of recurrence of atrial fibrillation (18). The observation that most recurrences occur during the same time period as remodeling supports this view (18). Some studies however have observed AF recurrence despite the presence of reverse atrial electrical remodeling. Manios et al found that atrial refractoriness in the right atrial appendage had normalized within 24 hours post cardioversion, yet the AF recurrence rate was 11%

within 24 hours, as compared to 32% which recurred later (16). Similarly, Fynn et al found AF recurrence despite the presence of reverse atrial electrical remodeling. (19).

Given the temporal changes in refractoriness following cardioversion, it is likely that dispersion of refractoriness following cardioversion is a dynamic rather than a static process. If dispersion is dynamic, it would seem that space and time would be important factors to consider in studying the association between atrial refractoriness and the recurrence of AF. Therefore, I hypothesized that a greater change in dispersion of refractoriness would be associated with an increase in the risk of atrial fibrillation recurrence following cardioversion.

To test this hypothesis, I measured the atrial effective refractory period at three atrial sites at two different time points after cardioversion in patients with persistent AF. I examined the relationship between the changes in atrial refractoriness over time, differences in refractoriness between atrial sites (dispersion), and change in dispersion over time to the recurrence of AF.

Methods

Overview

A group of patients underwent internal cardioversion of AF and had electrophysiological measurements made immediately after cardioversion and repeated at one hour. The patients were followed for 6 months for recurrence of atrial fibrillation. An outline of the study is shown in figure 1.

Figure 1:

Study Outline

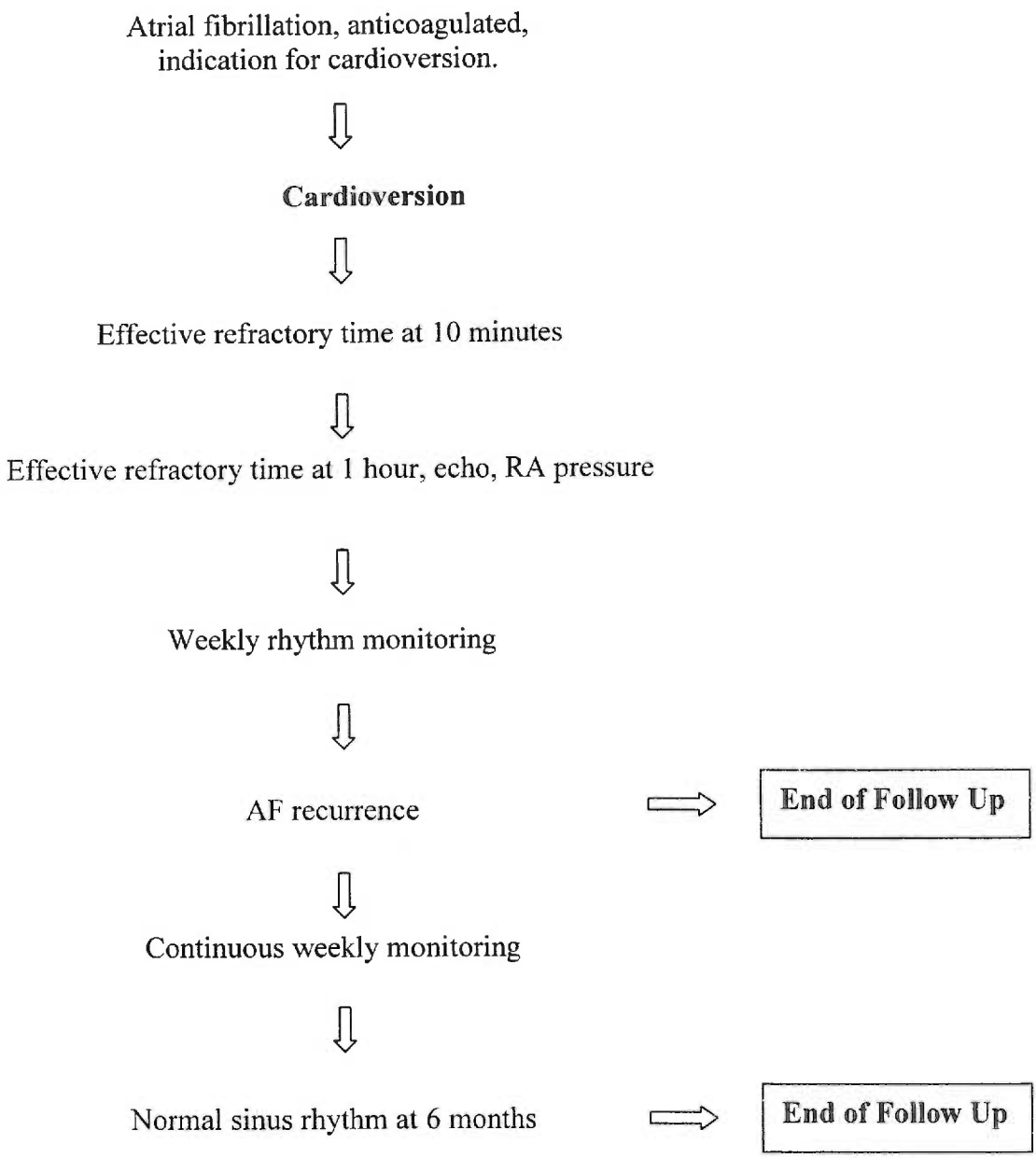


Figure 1 shows the study outline.

Electrophysiological measurements done in patients with and without AF recurrence were compared. The difference between 10 minute measurements of ERP and one hour measurements of ERP, dispersion of refractoriness, and change in dispersion of refractoriness were compared between patients with and without AF.

The cohort was divided into patients who had a greater change in dispersion of refractoriness (above the median) and into patients who had a smaller change in refractoriness (below the median). The rate of AF recurrence was compared between the group of patients above and the group of patients below the median change in dispersion. The cohort was also divided into patients who exhibited varying proportions of the atria which exhibited reverse electrical remodeling as determined by an increase in ERP.

Data analysis included: 1) A determination of whether an increasing change in dispersion of refractoriness is associated with early recurrence of atrial fibrillation, 2) A determination of whether varying proportions of atrial sites exhibiting an increase in refractory period is associated with early recurrence of atrial fibrillation, 3) A comparison of these parameters to each other and to clinical factors for the prediction of AF recurrence.

Patient Selection

The study was carried out on 40 consecutive patients who were referred for cardioversion of persistent atrial fibrillation and agreed to the study. Persistent atrial fibrillation was defined as atrial fibrillation for greater than 30 days but less than 1 year. No patient had significant mitral valve disease or had cardiac surgery within the last 2

months. Patients were free of class I and class III antiarrhythmic therapy, verapamil and diltiazem 4 weeks prior to cardioversion. Patients with thyroid dysfunction were euthyroid as assessed by a TSH assay at the time of the electrophysiology study. No patient had undergone cardioversion 1 week prior to the study cardioversion.

The lack of regular P waves or flutter waves, and irregular RR intervals were used as criteria to diagnose atrial fibrillation. The study group came from the catchment area of the Portland VA Medical Center. The Portland VA Medical Center Institutional Review Board approved the study, and all of the patients gave informed written consent. Prior to consent to the study, patients had agreed to cardioversion of atrial fibrillation. I personally recruited all patients involved in the study and performed most of the electrophysiological studies with the help of Dr. Merritt Raitt.

Electrical Cardioversion

Elective intracardiac cardioversion was performed at the Portland VA Medical Center catheterization lab. The patients were sedated with midazolam and fentanyl. Three catheters were placed in each patient. A 6 Fr multipolar catheter was positioned along the lateral right atrial wall. A second 6 Fr multipolar catheter was placed in the coronary sinus. A third 6 Fr catheter was positioned in the right ventricular apex, and provided R wave synchronization for cardioversion. This catheter also provided back up ventricular pacing.

The right atrial and coronary sinus catheters were connected (right atrium negative, left atrium positive) to an external atrial defibrillator to give a truncated

biphasic exponential shock with the two phases each of 6 - 20 ms duration, with the phases separated by 240μs. Shocks were synchronized to the right ventricular trigger signal with a delay of 20 ms.. Shocks were initially delivered at 4 Joules with energy increased to 6 J, 12 J, 20 J, and 32 J if each cardioversion was not successful. Further internal shocks were no longer delivered when the patient converted to sinus rhythm or did not convert at 32 J. If the series of internal shocks failed to establish sinus rhythm, then external shocks were performed starting at 300 Joules and increased up to 720 Joules using two external defibrillators.

Electrophysiological Study

Data was collected 10 minutes and one hour after cardioversion. Data collection periods at 10 minutes and at 1 hour following cardioversion were used because we had previously shown a significant change in ERP at the right atrium within one hour following cardioversion. To reduce the influence of autonomic tone on the measurements of ERP, patients were given a total of 2 milligrams of atropine and 15 milligrams of metoprolol intravenously over 15 minutes.

The ERP was measured during continuous pacing at the site to be studied by introducing premature stimuli after every 8^{th} drive train complex. The coupling interval between the 8^{th} drive train complex and the premature stimuli started at 160 ms and was increased by 2 ms increments until atrial capture. For the second measurement, the procedure was repeated by decreasing the coupling interval to 10 ms below the capture interval and then increasing the coupling interval by 1 ms increments until atrial capture. The procedure was repeated by decreasing the coupling interval to 10 ms below the

capture interval and then increasing the coupling interval by 1 ms increments until atrial capture. A third measurement was performed using 1 ms increments starting at a coupling interval 10 ms below the second capture interval if the capture intervals of the first two measurements differed by more than 5 ms. This entire procedure was performed at drive train cycle lengths of 550 and 400 ms at 3 times the local pacing threshold at the high right atrium, the coronary sinus os, and at the distal coronary sinus beginning 10 minutes after cardioversion and repeated 1 hour after cardioversion. The order in which the right atrium, coronary sinus os, and distal coronary sinus sites were tested was chosen randomly but the same sequence was used for the 10 minute and 1 hour measurements. The ERP for each specific site and drive train cycle length was defined as the average of all the capture intervals. If capture of the atrium by a premature stimuli resulted in the introduction of sustained AF during the 10 minute testing session then the patient was cardioverted and testing begun at the next site. If AF was induced a second time, the patient was cardioverted and testing begun again 1 hour after the last cardioversion. If AF was induced during the 1 hour testing session no additional pacing was performed. Because of the induction of AF, difficulties with catheter position, or inadequate atrial pacing capture, not all patients have ERPs measured at all possible pacing sites and drive train cycle lengths.

I personally performed most cardioversions and electrophysiologic studies under the supervision of Dr. Merritt Raitt.

Follow Up

After cardioversion, cardiac rhythm was monitored for evidence of arrhythmias and to monitor drug affects of metoprolol, atropine, fentanyl, and midazolam for 4 hours using telemetry. The patient was given a transtelephonic monitor and was asked to call in an EKG rhythm strip once a week or more frequently in the event of symptoms suggestive of AF recurrence. Symptoms included palpitations, irregular pulse, or inappropriately rapid pulse. If a patient did not transmit a scheduled rhythm strip, the patient was contacted by telephone. If there was no response, the patients clinical status was followed using medical records of physician visits and any ECG obtained during follow up. Follow up was continued for 6 months or until a documented recurrence of AF.

Statistical Analysis

Based on historical controls, I expected to see a 50% recurrence rate post cardioversion at 6 months. Assuming an 85% recurrence rate in those who exhibited a greater change in dispersion of refractoriness, the null hypothesis would be successfully rejected at 0.8 with a significance level α=0.05 with 38 patients.

The change in refractoriness over time was evaluated by comparing the mean ERP at each site (high right atrium, coronary sinus os, and distal coronary sinus) and cycle length during the 10 minute and during the 1 hour data collection period. The mean change in ERP at 10 minutes was compared to 1 hour using the students t test for patients

with atrial fibrillation recurrence and for patients without recurrence following cardioversion at each site and each cycle length.

Since reverse atrial electrical remodeling may progress at different tempos at different locations within the atria, the proportion of the atria demonstrating an increase in atrial refractoriness was examined. The proportion of the total atria (left and right atrium) undergoing an increase in the atrial refractoriness was calculated to reflect the reverse remodeling process in a single measure for the entire atria. The reverse remodeling proportion was calculated by dividing the number of atrial sites which demonstrated reverse remodeling by the total number of measured sites and cycle lengths of pacing. A 2 milliseconds change (one half the standard error of the mean) was considered a clinically significant increase for this analysis. The recurrence of AF was compared between groups at different reverse atrial electrical remodeling proportions using cross tabs and a chi square statistic. Minimal reverse atrial electrical remodeling was defined as less than 25% of the measured sites and cycle lengths demonstrating a 2 millisecond increase in ERP over 1 hour (remodeling proportion < 0.25). Heterogeneous reverse atrial electrical remodeling was defined as greater than or equal to 25% of the atria but less than or equal to 75% of the atria demonstrating a 2 millisecond increase in ERP over 1 hour (0.25<=remodeling proportion < =0.75). Homogeneous reverse atrial electrical remodeling was defined as greater than 75% of the atria demonstrating a 2 millisecond increase in ERP over 1 hour (remodeling proportion >0.75). Since remodeling proportion and recurrence of AF had a nonlinear relationship, a transformation was performed where heterogeneous remodeling patients were compared to a combined group of homogeneous and minimal atrial electrical remodeling. This

transformation was used in the analysis of recurrence, logistic regression, and the Cox regression.

Spatial differences in refractoriness were evaluated by examining dispersion of refractoriness. Dispersion of refractoriness was defined as the difference between the maximum and minimum ERP measured at various atrial sites for each drive train cycle length at each time point. Dispersion was compared between patients who had atrial fibrillation recurrence versus patients without atrial fibrillation recurrence.

The spatial change of refractoriness over time was evaluated by examining the change in dispersion. Change in dispersion was calculated as the absolute difference in dispersion between 10 minutes and at 1 hour.

Change in Dispersion =

$$\left| \text{maximum ERP difference at 1 hour} - \text{maximum ERP difference at 10 minutes} \right|$$

The absolute value was used for the difference between dispersion at 1 hour and 10 minutes because, whether this value is positive or negative, there would eventually be a progressive increase in dispersion over time (figure 12).

The change in dispersion at both pace drive train cycle lengths was compared in patients with atrial fibrillation recurrence versus those without recurrence. The relationship of the recurrence of atrial fibrillation to the change in dispersion was further examined by comparing the group above the median to the group below the median.

A comparison between the reverse remodeling proportion and the change in dispersion was performed. Since the relationship between remodeling proportion and recurrence of AF appeared to be such that the risk was highest with heterogeneous reverse remodeling (reverse remodeling proportion between 0.25 and 0.75) and lower for either smaller reverse remodeling proportion (minimal reverse remodeling) or larger reverse remodeling proportion (homogeneous remodeling), a transformation was created so that the risk of AF could be linearly related to the remodeling proportion. Since maximal heterogeneous reverse remodeling is 0.5, remodeling proportions close to 0.5 are likely related to a greater change in dispersion. While remodeling proportions closer to 0 or 1 are likely related to less change in dispersion. Therefore the transformation consisted of subtracting 0.5 from the remodeling proportion and taking the absolute value.

$$\text{Modified Remodeling Proportion} = |\text{Remodeling Proportion} - 0.5|$$

The modified remodeling proportion was correlated with change in dispersion at cycle length 550 ms using a Pearson correlation to evaluate whether they are measuring similar electrical parameters.

A two sided chi square statistic was used for comparisons in patients with categorical variables and a two sided t test for analysis of continuous variables. An independent sample two sided t test was used for analysis of data presented in table 4. A two sided t test was used for analyses of data displayed in tables 6, 7, 8 and 9.

A multivariate analyses using clinical and electrophysiological parameters in predicting the recurrence of AF was performed. The independent variables included: the presence of heterogeneous reverse atrial electrical remodeling proportion and change in dispersion of greater than 10 ms which was compared to left atrial diameter (parasternal long axis) greater than 50 mm, age greater than 70 years, coronary artery disease, obstructive lung disease, hypertension, diabetes, AF induction during electrophysiological testing, right atrial pressure greater than 10 mm, and dispersion above the median at both cycle lengths. The presence of coronary artery disease, obstructive lung disease, hypertension, and diabetes was determined by clinical review of the chart and by interviews with the patient.

The dependent variables included the presence or absence of atrial fibrillation at follow up, and time to recurrence of atrial fibrillation. A forward stepwise logistic regression was used to propose a model to determine which electrophysiological and clinical parameters are the strongest predictors of AF recurrence at 6 months. Variables that were significant, $p< 0.05$, were used as entry criteria into the stepwise logistic regression analysis. The number of days to AF recurrence using the presence of heterogeneous reverse atrial electrical remodeling proportion and change in dispersion of greater than 10 ms was compared to left atrial diameter (parasternal long axis) greater than 50 mm, age greater than 70 years, coronary artery disease, obstructive lung disease, hypertension, diabetes, AF induction during electrophysiological testing, right atrial pressure greater than 10 mm, and dispersion above the median at both cycle lengths was evaluated using a Cox regression.

Results

Patients

Table 1 shows the clinical characteristics of the study group. The study group were men with a mean age of 71.1 ±3.3 years who had AF for greater than 90 days. Eleven patients had a history of atrial fibrillation. The left atrial diameter was not markedly enlarged in this group (43.0±12.2 mm). A large proportion of these patients had underlying cardiovascular disease including history of congestive heart failure (20%), hypertension (55%), coronary artery disease (47.5%), myocardial infarction (22.5%), coronary bypass surgery (22.5%) and cerebrovascular accident (12.5%). Many patients had diabetes which all were type II (30%), and chronic obstructive pulmonary disease (17.5%). A small portion of patients had lone atrial fibrillation (17.5%). Most patients were receiving ß-blockers (75%), and some patients were receiving ace inhibitors (35%), and dihydropyridine calcium channel blockers (8%).

Table 1. Clinical Data of the Studied Patients

	Whole group (n=40)
Age, y	71.1±3.3
LA diameter, mm	43.0±12.5
Right atrial pressure, mm Hg	11.1±1.2
Pulmonary capillary wedge pressure, mm Hg	12.8±4.9
History of congestive heart failure, n	8 (20)
Hypertension, n	22 (55)
Coronary artery disease, n	19 (47.5)
Myocardial infarction, n	9 (22.5)
Coronary Artery Bypass Grafting, n	9 (22.5)
Cerebrovascular Accident, n	5 (12.5)
Diabetes, n	12 (30)
Chronic obstructive pulmonary disease, n	7 (17.5)
Lone AF, n	7 (17.5)
β-blockers, n	30 (75)
Angiotensin converting enzyme inhibitor, n	14 (35)
Dyhydropyridine calcium channel blockers, n	3 (8)

Shown above are the clinical characteristics of the study population, n=number, y=years, d=days, and LA= left atrial. Continuous variables are expressed as mean ± standard deviations. Categorical variables are shown as number and percentage of whole group in parenthesis.

Out of 40 patients, two patients were unable to maintain sinus rhythm for 10 minutes immediately following cardioversion. Therefore the measurement protocol was carried out in 38 patients at 10 minute data collection period. Since three patients had AF between the 10 minute data collection period and 1 hour data collection period and were

subsequently unable to be cardioverted to sinus rhythm, the measurement protocol was carried out in 35 patients at 1 hour following cardioversion. Nonsustained atrial fibrillation was induced in 14 patients and sustained atrial fibrillation requiring cardioversion in 5 patients. In 24 patients, refractory measurements were obtainable at all 3 sites. The number of patients with obtainable ERPs at each location and cycle length are displayed on table 2.

Table 2. No. of Obtainable Refractory Period at Each Site for both 10 Minutes and 1 Hour

	Lateral right atrium	Coronary sinus os	Distal coronary sinus
Cl 550, n	32	29	24
Cl 400, n	30	26	22

Shown above are the number of obtainable measurements out of 40 patients, Cl=cycle length and n= number of patients. There were fewer measurements in the distal coronary sinus because of difficulties in cannulating the coronary sinus. When multivariate analysis was limited to patients where ERP measurements were made at all three sites, the results did not change.

There were follow up rhythm strips available for review in all study patients. Out of 19 patients who had documented sinus rhythm on follow up, 15 patients completed at least 150 days of follow up. All patients with recurrence of AF had confirmation of their rhythm.

Atrial refractoriness is a multidimensional variable which changes over time and space following cardioversion. The change in refractoriness over time at all measured atrial sites was examined in relation to recurrence of AF. Spatial differences in refractoriness at two different time points in relation to AF recurrence were also examined. Finally the change in dispersion which combined spatial and temporal changes in refractoriness over time were examined in relationship to AF recurrence.

Changes of Refractoriness over Time

Reverse atrial electrical remodeling was observed at the high right atrium but not at other locations. At the high right atrial site the mean ERP increased from 10 minutes to 1 hour, from 216.3±3.7 to 223.7±4.9 ($p=0.005$) ms and from 209.5±4.2 to 214.9±4.7 ms ($p<.001$) at cycle lengths 550 ms and 400 ms respectively. There was no difference in the ERP at 10 minutes compared to 1 hour at the distal coronary sinus or at the coronary sinus os (table 3). Reverse atrial electrical remodeling at the right atria alone did not predict atrial fibrillation recurrence (table 4).

Table 3. Effective Refractory Period in the Atria at 10 Minutes and 1 Hour

	ERP measured at 10 Minutes, ms	ERP measured at 1 Hour, ms	
High right atrium Cl 550, n=32	216.3±3.7	223.7±4.9	p<0.005
High right atrium Cl 400, n=30	209.5±4.2	214.9±4.7	p<0.001
Coronary sinus os Cl 550, n=29	223.6±4.2	225.6±5.2	p=0.409
Coronary sinus os Cl 400, n=26	211.6±4.0	213.6±4.2	p=0.446
Distal coronary sinus Cl 550, n=24	224.6±5.0	224.1±5.2	p=0.789
Distal coronary sinus Cl 400, n=22	203±5.0	201.8±5.1	p=0.591

Shown above are the effective refractory periods (ERP) at 10 minutes and 1 hour at both cycle lengths (Cl). Reverse atrial electrical remodeling as reflected by a change in ERP was observed in the high right atrium, but not at the other measured sites. Paired T tests comparing the ERP between 10 minutes and 1 hour were performed at each cycle length.

Table 4. Reverse Atrial Electrical Remodeling at the High right atrium at Cl 550 and Cl400 and Atrial Fibrillation Recurrence

	Atrial Fibrillation Recurrence	No Recurrence	p value
High right atrium Cl 550, ms	10.7	5.0	0.272
High right atrium Cl 400, ms	2.5	2.1	0.602
Coronary sinus os Cl 550, ms	.18	3.7	0.488
Coronary sinus os Cl 400, ms	2.5	2.1	0.936
Distal coronary sinus Cl 550, ms	-1.9	.85	0.478
Distal coronary sinus Cl 400, ms	-1.2	-1.4	0.967

Table shows average ERP differences between 10 minutes and 1 hour at various locations and cycle lengths (Cl). Positive values indicate an increase in the ERP between 10 minutes and 1 hour. Although reverse atrial electrical remodeling occurred at the high righ atrium these temporal changes in the ERP at the high right atrium did not predict recurrence of atrial fibrillation. An independent sample t test was used to compare groups.

The proportion of the atria undergoing reverse atrial electrical remodeling was evaluated in relation to AF recurrence. Twenty eight out of 35 patients had some evidence of reverse atrial electrical remodeling with some part of the atrium demonstrating an increase in the ERP (>2ms) between 10 minutes and 1 hour at either cycle length (400 ms or 550 ms). The proportion of atria at all measured sites and cycle lengths undergoing reverse remodeling were divided into upper 25%, middle 50% and lower 25%. Minimal reverse atrial electrical remodeling, defined as less than 25% of the measured sites and cycle lengths, demonstrated a 2 millisecond increase in ERP over 1 hour (remodeling proportion < 0.25). Heterogeneous reverse atrial electrical remodeling, defined as greater than 25% of the atria but less than 75% of the atria, demonstrated a 2

millisecond increase in ERP over 1 hour (0.25<=remodeling proportion < 0.75). Homogeneous reverse atrial electrical remodeling, defined as greater than 75% of the atria, demonstrated a 2 millisecond increase in ERP over 1 hour (remodeling proportion >0.75). The number of patients in each of these groups who had recurrence of AF is shown in table 5. A low number of patients with either minimal reverse atrial remodeling or homogeneous reverse atrial electrical remodeling had a recurrence of AF (minimal reverse atrial electrical remodeling: 1/8 patients with a reverse remodeling proportion of <. 25 had an AF recurrence; homogeneous reverse atrial electrical remodeling: 1/8 patients with a reverse remodeling proportion of >.75 had an AF recurrence RR=0.857, p=0.919). A high number of patients with heterogeneous reverse atrial electrical remodeling had recurrence of AF (15/19 patients with AF recurrence, RR=22.5, p=0.003).

Table 5: Atrial Fibrillation Recurrence in Patients at Different Reverse Atrial Electrical Remodeling Proportions.

Reverse Remodeling Proportion	Atrial fibrillation	No Atrial Fibrillation Recurrence	Crude Relative Risk	p value
<. 25 of atria undergoes reverse atrial electrical remodeling	1	7	1	
.25<= x<=. 75 of atria undergoes reverse atrial electrical remodeling	15	4	22.5	0.003
>.75 of atria undergoes reverse atrial electrical remodeling	1	7	.857	0.919

The proportion of atria at all measured sites and cycle lengths undergoing reverse remodeling are displayed in upper 25%, middle 50% and lower 25%. Patients with remodeling proportion less than 0.25 were considered to have minimal atrial electrical remodeling. Patients with remodeling proportion greater than or equal to 0.25 but less than or equal to 0.75 were considered to have heterogeneous atrial electrical remodeling. Patients with remodeling proportion greater than 0.75 had homogeneous reverse atrial electrical remodeling. Univariate logistic regression revealed that patients with heterogeneous reverse atrial electrical remodeling were at high risk of atrial fibrillation recurrence. The lower 25% reverse remodeling proportion is used as the reference group in this table.

Dispersion of Refractoriness

Spatial differences in refractoriness were present at 10 minutes and 1 hour following cardioversion. The ERP was significantly different at the high right atrium and the distal coronary sinus at 10 minutes at both cycle lengths. At 1 hour following cardioversion, there continued to be a significant difference in the mean ERP between the high right atrium and the distal coronary sinus at cycle length 400 but not at cycle length 550 ms (table 6). The other sites had less consistently statistically significant differences in the mean ERP.

Table 6: Differences in mean ERPs between different locations at various cycle lengths

Paired sites and cycle lengths	Mean difference of ERP between the paired sites	p value
10 Minutes		
CI 550		
Right atrium vs. coronary sinus os, ms	-5.9048	0.100
Coronary sinus os vs. distal coronary sinus, ms	-4.0476	0.303
Right atrium vs. vs distal coronary sinus, ms	-9.9524	0.031
CI 400		
Right atrium vs. coronary sinus os, ms	0.8276	0.806
Coronary sinus os vs. distal coronary sinus, ms	6.3933	0.064
Right atrium vs. vs. distal coronary sinus, ms	9.5917	0.010
1 Hour		
CI 550		
Right atrium vs. coronary sinus os, ms	0.9943	0.832
Coronary sinus os vs. distal coronary sinus, ms	-3.3750	0.471
Right atrium vs. distal coronary sinus, ms	-2.8478	0.552
CI 400		
Right atrium vs. coronary sinus os, ms	6.1200	0.091
Coronary sinus os vs. distal coronary sinus, ms	10.3596	0.022
Right atrium vs. distal coronary sinus, ms	12.6250	0.007

Spatial differences in refractoriness (dispersion of refractoriness) at 10 minutes and 1 hour as reflected by differences in mean ERP between various locations at both cycle lengths are shown above. A two sided t test was performed between each pair of sites. Dispersion of refractoriness was present at 10 minutes at both cycle lengths (CI). At 1 hour, dispersion of refractoriness was not present at cycle length 550, but was present at cycle length 400.

Spatial differences in refractoriness at 10 minutes and 1 hour following cardioversion in relationship to AF recurrence was examined. The widest ERP difference between any 2 sites at a given cycle length was used as a measure of dispersion of

refractoriness. Overall, there was not a significant difference in dispersion of refractoriness between 10 minutes and 1 hour following cardioversion (table 7). Dispersion of refractoriness at cycle length 550 ms at 10 minutes and 1 hour following cardioversion were not different between patients with atrial fibrillation recurrence versus patients without atrial fibrillation recurrence. Dispersion of refractoriness at cycle length 400 ms at 10 minutes after cardioversion was less in patients who had AF recurrence. However at 1 hour following cardioversion, dispersion of refractoriness was similar at both drive train cycle lengths in patients with or without atrial fibrillation recurrence versus those without recurrence (table 8 & 9, figure 2-5).

Table 7: Comparison of Dispersion of Refractoriness at 10 Minutes vs. 1 Hour

	10 Minutes	1 Hour	p value
Cycle length 550, ms	22.8	23.0	0.936
Cycle length 400, ms	16.3	18.3	0.448

Spatial differences in refractoriness as reflected by the mean dispersion of refractoriness (widest atrial ERP difference between measured sites) of all patients at 10 minutes and at 1 hour. A two sided paired sample t test was performed between 10 minutes and 1 hour. There was not a significant difference between the mean dispersion at 10 minutes and 1 hour.

Table 8: Dispersion of Refractoriness in Relation to Recurrence of Atrial Fibrillation at 10 Minutes.

	Atrial Fibrillation Recurrence	No Atrial Fibrillation Recurrence	p value
Cycle length 550, ms	24.5	23.5	0.831
Cycle length 400, ms	11.8	21.7	0.025

Spatial changes using widest mean ERP difference at 10 minutes as a measure of dispersion of refractoriness did not predict recurrence of atrial fibrillation at cycle length 550 ms. At cycle length 400 ms, there was decreased dispersion in patients with atrial fibrillation recurrence. A two sided independent samples t test was used to compare means.

Table 9: Dispersion of Refractoriness in Relation to Recurrence of Atrial Fibrillation at 1 Hour.

	Atrial Fibrillation Recurrence	No Atrial Fibrillation Recurrence	p value
Cycle length 550, ms	24.5	21.3	0.58
Cycle length 400, ms	18.8	17.8	0.85

Spatial changes using widest mean ERP difference as a measure of dispersion of refractoriness at 1 hour did not predict recurrence of atrial fibrillation. The difference in dispersion at 10 minutes at cycle length 400 ms seen between patients who had recurrence of atrial fibrillation versus those who did not have recurrence was no longer present at 1 hour. A two sided t test was used to compare means.

Figure 2:

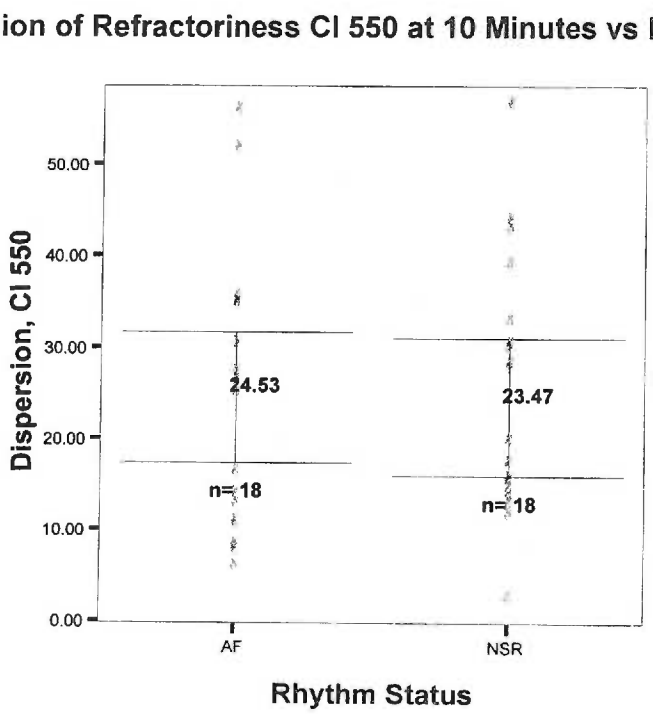


Figure 2: Comparison of dispersion of refractoriness at cycle length (CI) 550 ms in patients with atrial fibrillation (AF) recurrence versus patients without atrial fibrillation recurrence. At 10 minutes, there was no difference in dispersion of refractoriness between patients with AF recurrence versus those without AF recurrence (NSR). Means and 95% confidence intervals are shown.

Figure 3:

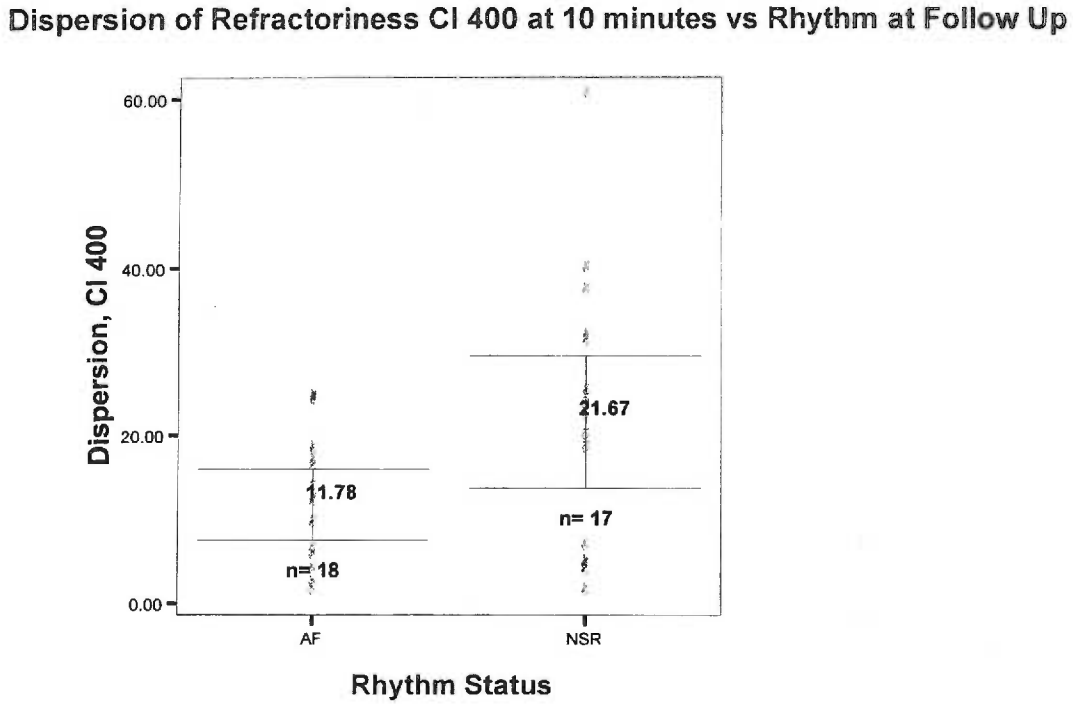


Figure 3: Comparison of dispersion of refractoriness at cycle length (Cl) 400 ms in patients with atrial fibrillation recurrence versus patients without atrial fibrillation recurrence. At 10 minutes, patients with normal rhythm (NSR) during follow up had more dispersion compared to patients with AF recurrence. Means and 95% confidence intervals are shown.

Figure 4:

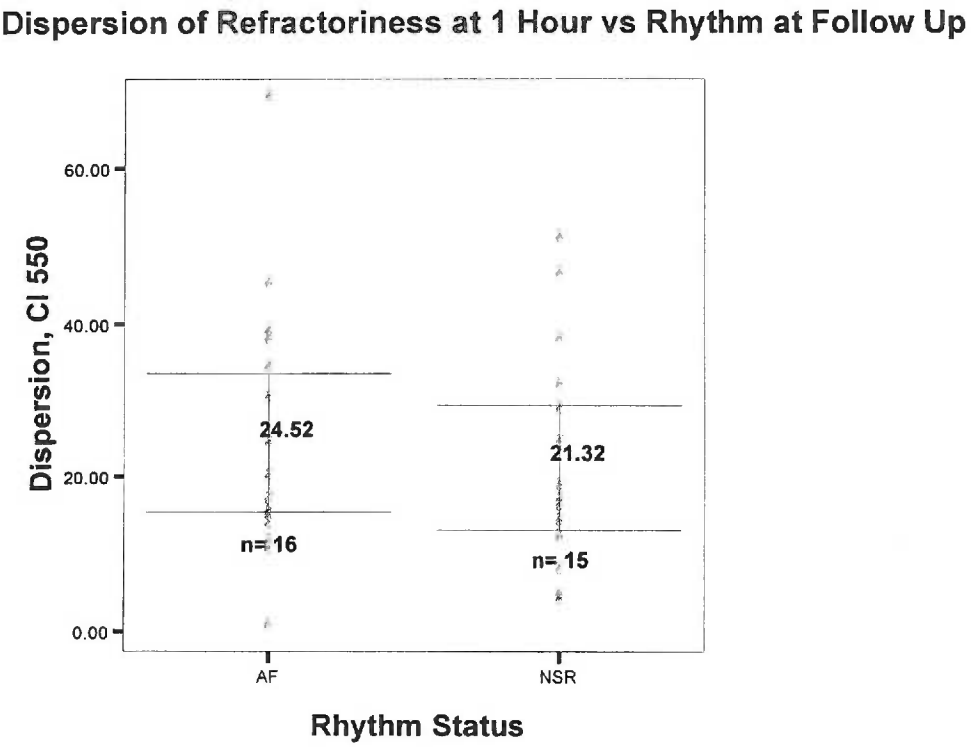


Figure 4: Comparison of dispersion of refractoriness at cycle length (Cl) 550 ms in patients with atrial fibrillation recurrence versus patients without atrial fibrillation recurrence. At 1 hour, there was no difference in dispersion of refractoriness between patients with AF recurrence versus those without AF recurrence (NSR). Means and 95% confidence intervals are shown.

Figure 5:

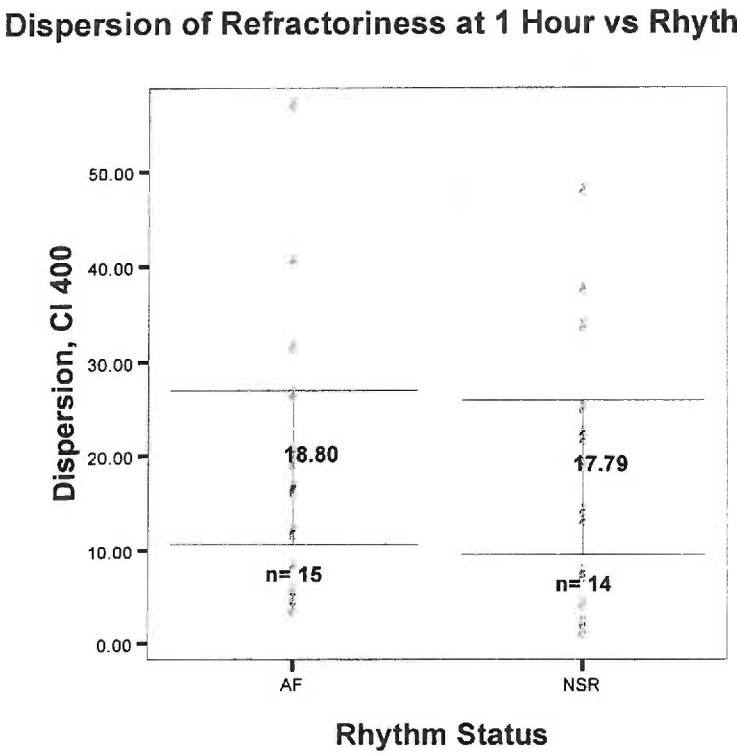


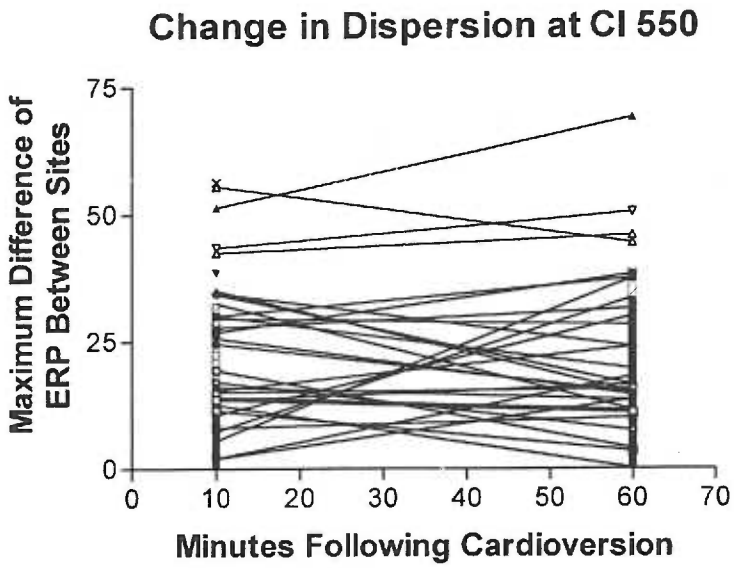
Figure 5: Comparison of dispersion of refractoriness at cycle length (CI) 400 ms in patients with atrial fibrillation recurrence versus patients without atrial fibrillation recurrence. At 1 hour, there was no difference in dispersion of refractoriness between patients with AF recurrence versus those without AF recurrence (NSR). Means and 95% confidence intervals are shown.

Change in Dispersion of Refractoriness Over Time

Change in dispersion of refractoriness over time was examined in relationship to AF recurrence. The change in dispersion was calculated as the absolute difference in dispersion between 10 minutes and 1 hour following cardioversion. The entire group had

a mean change in dispersion of 10.8 ms and 10.1ms at cycle lengths 550 ms and 400 ms respectively, between the 10 minute and 1 hour measurement. The change in dispersion at cycle length 550 ms. for the entire study group is shown in Figure 6. At cycle length 550 ms, there was significantly more change in dispersion in patients with atrial fibrillation recurrence than in patients without recurrence (p=0.007). However at cycle length 400 ms, there was no difference in the change in dispersion in patients with atrial fibrillation recurrence compared to patients without recurrence.

Figure 6



Change in maximum effective refractory period (ERP) differences between 10 minutes and 1 hour of the entire group at cycle length (Cl) 550ms. The study group had a wide range of change in dispersion of refractoriness between 10 minutes and 1 hour as reflected by different slopes for each patient.

To further evaluate the change in dispersion, the cohort was split in half using the median change in dispersion (Cl 550:10ms, Cl 400: 6.6 ms). The group above the median was compared to the group below the median in terms of AF recurrence. In 16

patients, the change in dispersion was greater than 10 ms at Cl 550. In this group, the risk of recurrence of atrial fibrillation was significantly increased compared to the patients with a change in dispersion of less than or equal to 10 ms (RR=9, p=0.007) (table 10, figure 7). Whether the change in dispersion was positive (7 patients) or negative (9 patients) there was an increased risk of atrial fibrillation recurrence (positive RR=2.6, p=0.046; negative RR=9.6, p=0.013). At cycle length 400, the change in dispersion was greater than 6.6 ms in 14 patients. In this group, there was no difference in the risk of recurrence of atrial fibrillation compared to the patients with an absolute change in dispersion of less than or equal to 6.6 ms (table 10, figure 8).

Figure 7:

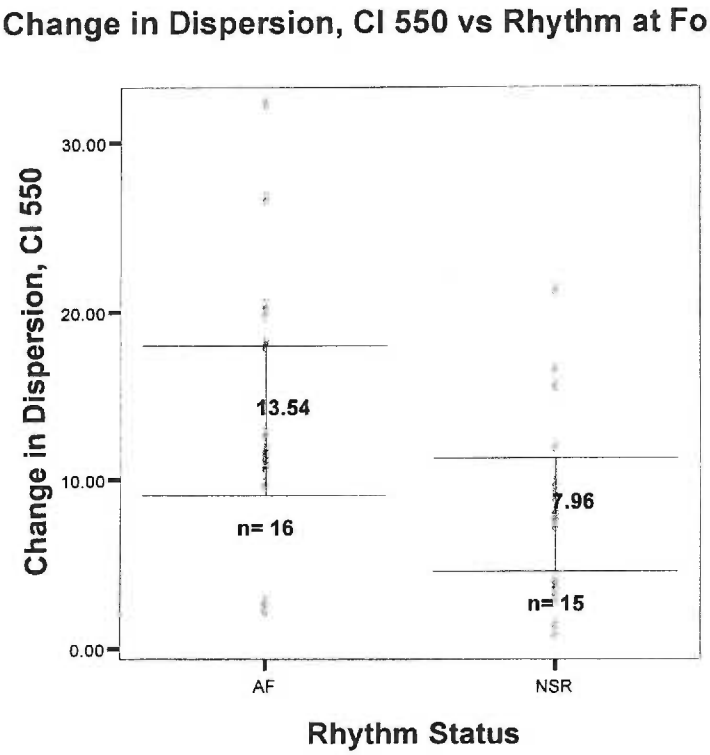


Figure 7: Comparison of change in dispersion at cycle length (Cl) 550 ms in patients with atrial fibrillation recurrence versus those with no recurrence. At cycle length 550 ms, patients with AF recurrence had a greater change in dispersion between 10 minutes and 1 hour. Means and 95% confidence intervals are shown.

Figure 8:

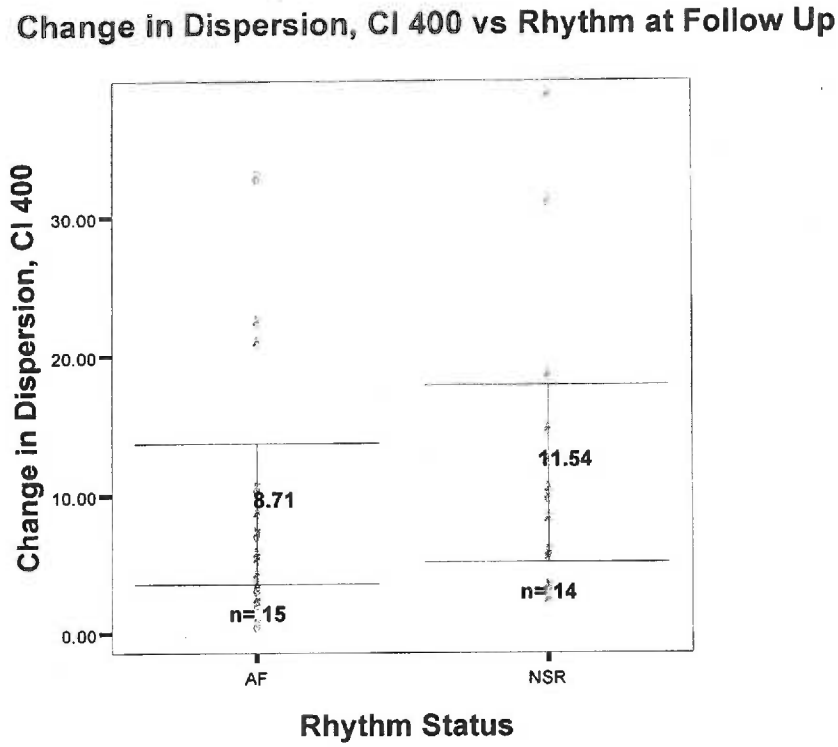


Figure 8: Comparison of change in dispersion at cycle length 400 ms in patients with atrial fibrillation recurrence versus those with no recurrence. At cycle length 400 ms, there was no difference in change in dispersion between patients with (AF) and without (NSR) AF recurrence. Means and 95% confidence intervals are shown.

Table 10. Change in Dispersion of Refractoriness Between 10 Minutes and 1 Hour

Change in Dispersion,	Atrial fibrillation recurrence	Normal sinus rhythm	Relative Risk for AF	p value
Above the median change in dispersion, Cl 550, n	12	4	9	0.007
Below the median change in dispersion, Cl 550, n	4	11	1	
Above the median change in dispersion, Cl 400, n	6	8	2	0.466
Below the median change in dispersion, Cl 400, n	9	6	1	

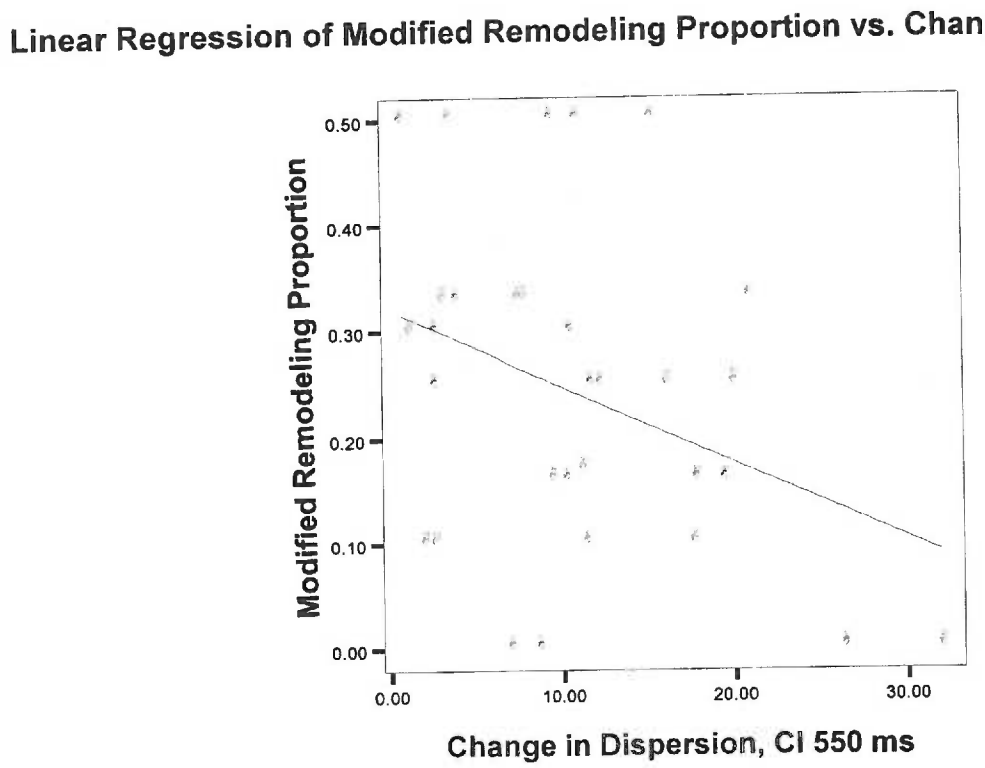
Spatial changes over time as reflected by change in dispersion of refractoriness. Change in dispersion was calculated by: absolute value (maximum ERP difference at 1 hour – maximum ERP difference at 10 minutes). The change in dispersion at cycle length (Cl) 550ms was highly predictive of atrial fibrillation recurrence. While the change in dispersion at cycle length (ms) 400 ms was not predictive of AF recurrence. Chi square statistic was used to compare groups.

Comparison of Reverse Atrial Electrical Remodeling to Change in Dispersion

Because the reverse atrial electrical remodeling proportion and the change in dispersion at 550 ms were statistically the strongest predictors of recurrence of atrial fibrillation, a comparison between these two variables was performed. Since the remodeling proportion has a nonlinear relationship to change in dispersion cycle length (Cl) 550 ms, a transformation was performed. The modified remodeling proportion equaled the absolute value of 0.5 – the remodeling proportion. Modified remodeling proportion = | 0.5 – remodeling proportion |. Therefore, a modified remodeling

proportion of zero is at maximal heterogeneous reverse atrial electrical remodeling (remodeling proportion=0.5). Patients with either minimal or homogeneous reverse atrial electrical remodeling will have an increased distance from heterogeneity. Linear regression of the change in dispersion versus the modified remodeling proportion resulted in the following equation: modified remodeling proportion = 0.32 – 0.01 (change in dispersion, Cl 550 ms). This linear regression of the change in dispersion at cycle length 550 ms versus the transformed remodeling proportion revealed a correlation (correlation coefficient = -0.335, P=0.05) (figure 9). Greater values in change in dispersion, Cl 550 ms tended to have a modified remodeling proportion closer to 0 (or a remodeling proportion closer to 0.5). In other words, patients with greater change in dispersion, Cl 550 ms tended to be patients who underwent heterogeneous reverse atrial electrical remodeling.

Figure 9



Because the remodeling proportion has a nonlinear relationship to change in dispersion cycle length (Cl) 550 ms, a transformation was performed. The modified remodeling proportion equaled the absolute value of 0.5 – the remodeling proportion. Modified remodeling proportion = | 0.5 – remodeling proportion |. Therefore, a modified remodeling proportion of zero is at maximal heterogeneous reverse atrial electrical remodeling (remodeling proportion=0.5). Patients with either minimal or homogeneous reverse atrial electrical remodeling will have an increased distance from heterogeneity. Linear regression of change in dispersion at cycle length 550 ms was related to the modified remodeling proportion by the following equation: modified remodeling proportion = 0.32 – 0.01 (change in dispersion, Cl 550 ms). The Pearson correlation was –0.355, P=0.05. Greater values in change in dispersion, Cl 550 ms tended to have a modified remodeling proportion closer to 0 (or a remodeling proportion closer to 0.5). In other words, patients with greater change in dispersion, Cl 550 ms tended to be patients who underwent heterogeneous reverse atrial electrical remodeling. While lesser values in change dispersion tended to have a greater distance from heterogeneity (remodeling proportion approaching either 0 or 1).

Comparison of Changing Refractory Properties to Clinical Variables in the Prediction of Atrial Fibrillation Recurrence Following Cardioversion

The following clinical variables were analyzed as predictors of atrial fibrillation recurrence: age, history of congestive heart failure, diabetes, hypertension, chronic obstructive pulmonary disease, history of stroke, history of coronary artery disease, history of myocardial infarction, previous coronary bypass grafting, right atrial pressure, left atrial size >50mm, atrial fibrillation induced during electrophysiological study, and presence of ß-blockers or ace inhibitors at the time of cardioversion. None of these clinical variables in a univariate analysis predicted atrial fibrillation recurrence following cardioversion (table 11).

Table 11: Univariate Logistic Regression of Clinical Variables in Predicting Atrial Fibrillation Recurrence

Variable	B	Odds ratio (upper, lower confidence intervals)	p value
Age (>70 years)	0.087	1.091 (.289, 4.122)	0.898
History of congestive heart failure	-0.644	0.525 (0.106, 2.603)	0.433
Diabetes	-0.256	0.774 (0.19, 3.16)	0.721
Hypertension	0.213	1.24 (0.344, 4.454)	0.744
Chronic obstructive pulmonary disease	-1.1	0.33 (0.055, 1.97)	0.223
History of stroke	9.51	13468 (0.0, 1.14e42	0.831
History of coronary artery disease	-.637	0.529 (0.146,1.92)	0.332
History of myocardial infarction	0.292	1.34 (0.298, 6.021)	0.703
Previous coronary artery bypass grafting	1.60	4.96 (0.873, 28.15)	0.071
RA pressure >10 mm Hg	-1.05	0.35 (0.075, 1.634)	0.182
B-blockers	1.135	3.11 (0.663, 14.589)	0.15
Angiotensin converting enzyme inhibitors	0.771	2.04 (0.518, 8.0)	0.308
Left atrial diameter >=50mm	-0.693	0.5 (0.069, 3.65)	0.5
AF induced during study	0 (both patients with AF induced vs. those without had no difference in AF recurrence)		0.869

Univariate analysis of each clinical variable in predicting AF is shown above.
B is the logistic regression coefficient for the variable, while exp (B) is an estimate of the odds ratio for the recurrence of AF. No clinical factors in univariate analysis were predictive of atrial fibrillation recurrence.

For the purpose of logistic regression, all variables were transformed into dichotomous variables. Continuous variables were dichotomized as follows: right atrial pressure >10 mm or <=10 mm, parasternal left atrial dimension >= 5.0 cm or < 5.0 cm, and age > 70 years or <=70 years. A multiple logistic regression model using all of these clinical variables and change in dispersion at both cycle lengths, showed that change in dispersion at cycle length 550, presence of heterogeneous remodeling and RA pressure >10 mm predicted recurrence of atrial fibrillation following cardioversion (table 12). A model utilizing only patients (n=22) where all three measurement sites were obtainable, yielded change in dispersion at cycle length 550 ms as the sole predictor of AF recurrence.

Table 12: Multiple Logistic Regression Analysis Using Clinical Variables, Presence of Heterogeneous Reverse Remodeling and Change in Dispersion of Refractoriness

	B	Exp(B)	Confidence Interval	Wald	P (if term removed)
Change in dispersion, Cl 550	23.62	1.8E+10	0, 2.9+295	.005	0.004
Presence of heterogeneous remodeling	23.19	1.2E+10	0, 2.9+295	.004	0.034
Right atrial Pressure >10mm Hg	34.299	7.9E+14	0, 2.9+295	.006	0.005

Forward stepwise logistic regression using either the Wald statistic and likelihood ratio resulted in the same model. B is the logistic regression coefficient for the variable, and exp (B) is an estimate of the odds ratio for predicting AF recurrence. Change in dispersion at cycle length 550ms, presence of heterogeneous reverse atrial electrical remodeling, and right atrial pressure >10 mm was highly predictive of atrial fibrillation recurrence in a multivariate analysis. Equation constant: -46.12 and -2log likelihood is – 3.819. The very large values for the odds ratio estimate are likely an artifact from small sample sizes. Although the association for each variable is important, the strength of the association for each variable cannot be evaluated in this analysis. All clinical variables from table 7 were also included in the model.

Time to Recurrence of Atrial Fibrillation Following Cardioversion

Figure 10 shows the timing of recurrence of AF in the total group. Most AF recurrences in the study group occurred within the first 10 days. A Cox proportional hazards regression model using the following variables was performed: age (categorized as >70 years or <=70 years, history of congestive heart failure, diabetes, hypertension, chronic obstructive pulmonary disease, history of stroke, history of coronary artery disease, history of myocardial infarction, previous coronary bypass grafting, right atrial pressure>10 mm Hg vs <= 10 mm Hg, dispersion of refractoriness above and below the median at both cycle lengths, and presence of ß-blockers or angiotensin converting enzyme inhibitors at the time of cardioversion, non-sustained atrial fibrillation during electrophysiologic testing, presence of heterogeneous reverse atrial electrical remodeling as a dichotomous variable, and change in dispersion between 10 minutes and 1 hour at cycle lengths 550 ms and 400 ms.

A forward stepwise Cox regression model showed that change in dispersion between 10 minutes and 1 hour at cycle length 550 ms was the strongest predictor of time to recurrence of atrial fibrillation (RR=12.23, p=0.02) (table 13). Figure 11 stratifies patients with greater change in dispersion (>10 ms) versus those with less change in dispersion (<10 ms) at the means of the covariates. A model utilizing only patients where all three measurement sites were obtainable yielded similar results.

Table 13: Multiple Cox Regression Model Using Clinical Variables, Presence of Heterogeneous Reverse Remodeling and Change in Dispersion of Refractoriness

	B	Exp (B)	Confidence Intervals	Wald	p
Change in dispersion, Cl 550	2.504	12.2	1.5, 100.7	5.4	0.02

The above table shows the Cox regression analysis. B is the Cox regression coefficient for the variable, and Exp (B) is an estimate of the relative risk for predicting time to AF recurrence. Absolute change in maximal ERP difference at cycle length (Cl) 550ms was highly predictive of the number of days until atrial fibrillation recurrence in a multivariate Cox Regression.

Figure 10

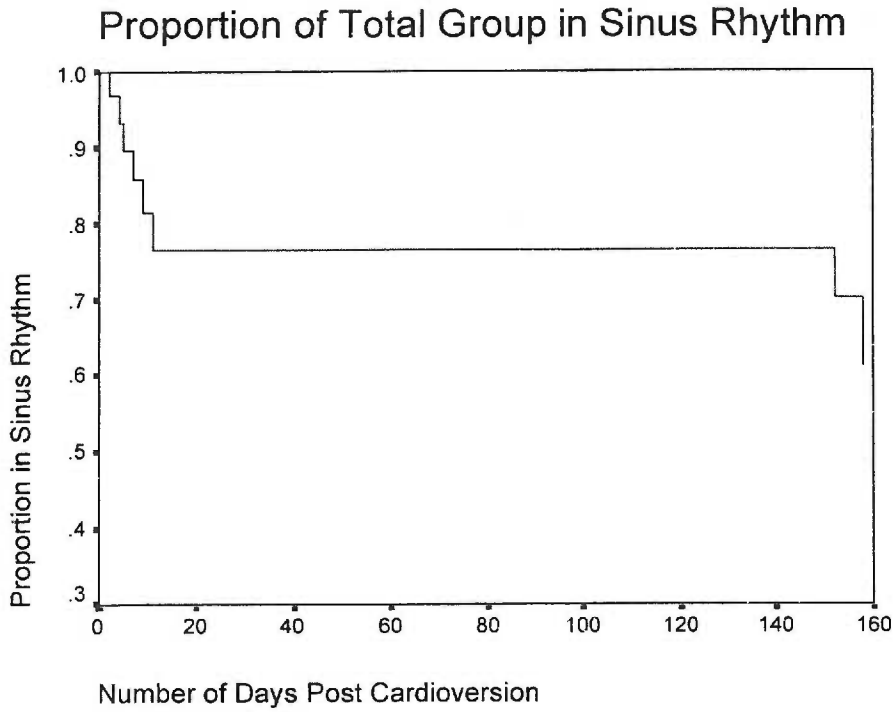


Figure 10: Recurrence of atrial fibrillation following cardioversion was highest in the first week for the entire group. In 5 months time, atrial fibrillation recurrence approach 55% for the entire group.

Figure 11

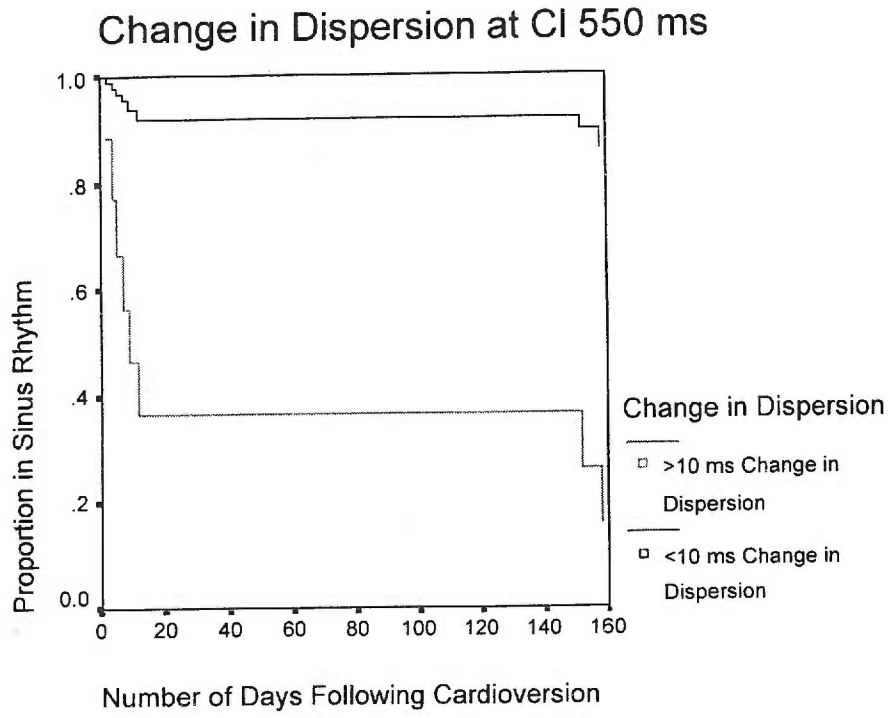


Figure 11: Greater change in maximum effective refractory period (ERP) difference between 10 minutes and 1 hour at cycle length (CI) 550 ms predicted a higher risk of early recurrence of atrial fibrillation. The Cox regression analysis took into account all of the clinical variables listed in the text.

Clinical Characteristics of Patients with Change in Dispersion and Heterogeneous Atrial Electrical Remodeling

There was no difference with patients who had a change in dispersion of greater than 10 ms versus those change in dispersion of less than 10 ms at cycle length 550 ms (table 14).

Table 14: Comparison of Clinical Parameters Between Different Groups.

	Change in Dispersion >, Cl 550 ms, n=16	Change in Dispersion <10ms, Cl 550 ms	p value
Age	71.4	71.5	0.960
LA diameter, mm	45.6	43.3	0.602
History of congestive heart failure, n	5(31)	1(6)	0.172
Hypertension, n	9(56)	9(56)	1.0
Coronary artery disease, n	7(44)	7(44)	1.0
Myocardial infarction, n	3(19)	2(13)	1.0
Coronary Artery Bypass Grafting, n	3(19)	3(19)	1.0
stroke, n	1(6)	3(19)	0.6
Diabetes, n	5(31)	5(31)	1.0
Chronic obstructive pulmonary disease, n	3(19)	3(19)	1.0
Lone AF, n	3(19)	2(125)	1.0
B-blockers, n	13(81)	10(63)	0.433
Angiotensin converting enzyme inhibitor, n	8(50)	3(19)	0.135
Right atrial pressure, mm Hg	12.2	9.6	0.197
Wedge pressure, mm Hg	10.5	11.5	0.817

Continuous variables are expressed as means. There was no significant difference between patients who had greater or lesser change in dispersion. Categorical variables are shown as number and percentage in parenthesis. P values for categorical variables are calculated using a two sided Fisher Exact Test. Two tailed t tests were used for continuous variables.

When heterogeneous reverse atrial electrical remodeling was compared to homogeneous and minimal reverse atrial electrical remodeling, there was no difference in clinical parameters between groups, with the exception of an increase prevalence of previous history of stroke in patients with homogenous or minimal reverse atrial electrical remodeling. However, this result should be examined with caution since the numbers in each cell are small (table 15).

Table 15: Clinical Characteristics at Various Reverse Remodeling Proportions.

	Heterogeneous Reverse Remodeling	Minimal or Homogeneous Reverse Remodeling	p value
Age	71.6	71	0.596
LA diameter, mm	46.7	41.7	0.225
History of congestive heart failure, n	5 (26)	3 (20)	1
Hypertension, n	10 (52)	10 (66)	0.495
Coronary artery disease, n	10 (53)	6 (40)	0.51
Myocardial infarction	3 (16)	3 (20)	1.0
Coronary Artery Bypass Grafting	2 (11)	5 (66)	0.199
Stroke, n	0	4 (27)	0.029
Diabetes, n	5 (56)	5 (66)	0.718
Chronic obstructive pulmonary disease, n	3 (16)	4 (27)	0.672
Lone AF, n	3 (16)	2 (13)	1.0
B-blockers, n	16 (84)	9 (60)	0.139
Angiotensin converting enzyme inhibitor, n	9 (47)	3 (20)	.152
Right atrial pressure	11.5 mm Hg	10.7 mm Hg	0.706
Wedge pressure	13.5 mm Hg	10.0 mm Hg	0.598

Patients who underwent homogenous electrical remodeling had a higher prevalence of previous stroke. Caution should be used, because of small cell sizes. Continuous variables are expressed as means. Categorical variables are shown as number and percentage in each group. T test was used to compare continuous variables between groups. Chi square statistic was used for categorical variables.

Discussion

In this study of patients with persistent AF, most recurrences of AF following cardioversion occurred within the first 10 days (78% in normal rhythm at 10 days, figure 10). Patients who have greater change in dispersion of refractoriness at cycle length 550

ms during the first hour following cardioversion are at increased risk of atrial fibrillation recurrence. This finding supports the hypothesis that a greater change in dispersion is associated with increased recurrence of AF. Patients with greater change in dispersion at cycle length 550 ms tended to have atrial fibrillation recurrence within the first week of cardioversion (figure 11).

The findings of this study are consistent with previous studies in that reverse atrial electrical remodeling was present during the first hour in the high right atrium following cardioversion. Although it has been postulated that reversal of this atrial electrical remodeling process will lead to less vulnerability to atrial fibrillation recurrence, we found that reverse atrial electrical remodeling at the high right atrium was not predictive of maintenance of normal rhythm or by inference, recurrence of AF. By multiple logistic regression analysis, heterogeneous reverse atrial electrical remodeling and right atrial pressure greater than 10 mm were also associated with recurrence of AF.

In the entire group, dispersion of refractoriness was present in the atrium, especially between the high right atrium and the distal coronary sinus 10 minutes following cardioversion. Others have observed that there is increased dispersion of refractoriness in patients with atrial fibrillation compared to controls, and it has also been suggested that this increased dispersion may predispose patients to an increased risk of atrial fibrillation (7). However in our study, dispersion of refractoriness at cycle length 550 ms at 10 minutes and 1 hour did not predict AF recurrence following cardioversion. Although at 10 minutes, dispersion of refractoriness was less in patients who had AF recurrence at cycle length 400 ms, by 1 hour, dispersion at this same cycle length was not predictive of atrial fibrillation recurrence. In the multivariate analysis, no measure of

dispersion at one point in time was predictive of the risk of recurrence. Because of reverse remodeling, the ERP and dispersion of refractoriness are changing over time. Therefore, an instantaneous measure of atrial vulnerability such as dispersion of refractoriness may not accurately reflect the risk of recurrence of atrial fibrillation in the ensuing days.

A change in dispersion of greater than 10 ms at cycle length 550 ms during the first hour was predictive of AF recurrence following cardioversion. The absolute value was used for the difference between dispersion at 1 hour and 10 minutes because, whether this value is positive or negative, there would be a progressive increase in dispersion over time. For a positive value, dispersion would become greater with time. For a negative value, although initially there would be lessening dispersion, eventually there would be greater dispersion once the trajectories crossed each other. Higher values of change in dispersion (whether positive or negative) would result in greater dispersion, or dispersion instability. For lower values of change in dispersion, there would less change in dispersion, or stable dispersion (figure 12). Dispersion instability may be why patients are vulnerable to atrial fibrillation recurrence in the first week following cardioversion.

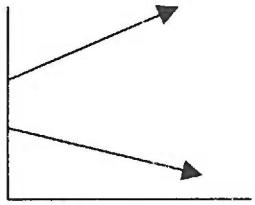
Figure 12:

Change in Dispersion Prior to Becoming an Absolute Value

A:

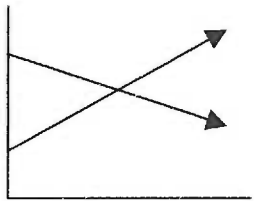
Positive Value

ERP Difference



Time

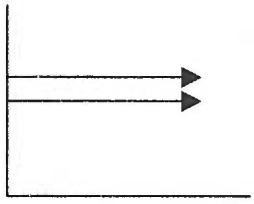
Negative Value ERP Difference



Time

B:

ERP Difference



Time

A: Prior to taking the absolute value of the difference in dispersions at 1 hour and 10 minutes, large values that are either positive or negative will eventually have greater dispersion. A positive value continues to have greater dispersion. A negative value will initially have less dispersion, but once the trajectories cross, this will result in greater dispersion. B: Smaller values of change in dispersion regardless of whether it is positive or negative will result in lesser change in dispersion or stable dispersion.

Change in dispersion was not predictive of AF recurrence when the ERP was measured at a drive train cycle length 400. This is probably due to a smaller change in

ERP at shorter paced cycle lengths compared to longer cycle lengths during atrial electrical remodeling. During atrial electrical remodeling there is abnormal shortening of ERP. However, this abnormal shortening is less at shorter paced cycle lengths compared to longer paced cycle lengths (21). As a result, during the reversal process, there is less change in ERP at shorter cycle lengths compared to longer cycle lengths. These smaller changes in ERP at short cycle lengths would also likely result in smaller changes in dispersion at similar cycle lengths. It is therefore not surprising that a change in dispersion at cycle length 400 ms compared to cycle length 550 ms was not a predictor of atrial fibrillation recurrence.

The spatial aspect of reverse atrial electrical remodeling was studied by using the reverse remodeling proportion. This method of quantifying the reversal of atrial electrical remodeling takes into account both atria and is very sensitive to increases in the ERP due to reverse remodeling. Patients who had homogeneous reverse atrial electrical remodeling or minimal reverse atrial electrical remodeling, where greater than 75% or less than 25% of the total atria underwent reverse atrial electrical remodeling respectively, were at low risk of AF recurrence. However, if heterogeneous reverse atrial electrical remodeling was observed, where reverse remodeling was observed in between 25% to 75% of the total atria, then patients were at increased risk of AF recurrence. These findings imply that heterogeneous reverse atrial electrical remodeling is more important than reverse atrial electrical remodeling in of itself in determining the risk of AF recurrence. Although it has been suggested that the atria remains vulnerable to further AF until reversal of atrial electrical remodeling is complete (9,22,23,24), it has been observed in other studies that despite the occurrence of reverse atrial electrical

remodeling, patients continued to have recurrences of atrial fibrillation (16,19). In determining atrial vulnerability following cardioversion, perhaps the spatial context of reverse atrial electrical remodeling is more important than the reversal of atrial electrical remodeling by itself.

Heterogeneous reverse remodeling and greater change in dispersion are related. Although the reverse remodeling proportion is very sensitive to reverse atrial electrical remodeling (using a 2 ms increase in ERP), it is likely that change in dispersion is a more sensitive measure of spatial changes of refractoriness over time especially as a predictor of atrial fibrillation recurrence. Since reverse atrial electrical remodeling was observed in the right atria but not in the left atrium in the first hour, it may be that this reversal process takes place at different rates in the right and left atrium or not at all at different locations in the atria. Varying amounts of reverse atrial electrical remodeling at different locations within the atria would be incorporated into a change in dispersion measurement. While the reverse remodeling proportion accounts only for an increase in refractoriness over time, change in dispersion accounts for an increase, decrease, or no change in refractoriness over time which may make it a better measure of spatial changes in refractoriness over time. This is supported by the observation that change in dispersion was a predictor of atrial fibrillation recurrence in both the logistic regression and the Cox regression while the presence of heterogeneous reverse atrial electrical remodeling was only a significant predictor of atrial fibrillation recurrence in the logistic regression analysis.

In agreement with previous studies, none of the historical clinical parameters considered in this thesis project predicted recurrence of atrial fibrillation (25-27). In

addition, the standard echo measure of left atrial size was not predictive of atrial fibrillation recurrence (28,29). However, right atrial pressure of greater than 10 mm was predictive of AF recurrence following cardioversion in the multivariate analysis but not in the univariate analysis. It has been previously postulated that atrial stretch may predispose patients to atrial fibrillation. Perhaps increased atrial pressure leads to atrial stretch and predisposes patients to AF.

None of the clinical factors considered in this study were significantly different in subgroups of patients who had a greater change in dispersion of refractoriness or had evidence of heterogeneous reverse atrial electrical remodeling compared to homogeneous or minimal reverse atrial electrical remodeling.

The findings of this study have important therapeutic implications. Identification of a high recurrence risk of AF may direct anti-arrhythmic therapy in specific patients. Taking into account change in dispersion may allow for development of new strategies directed at AF substrate modification (30).

Limitations

The study group consisted of older men who were all veterans of the United States Armed Forces and therefore the results of this study may not be broadly applicable. However, AF has a higher prevalence in older patients and sex differences in the electrophysiology of AF have not been previously observed. Measurements of ERP using the extra stimuli technique were not simultaneous. The extra stimuli technique was performed as rapidly as possible and in a randomly chosen order and was repeated in the

same random order at 1 hour. These techniques represent the state of the art at the point in time in which the study took place. Not all patients had ERP measurements at all atrial sites. However, when the analysis was limited to patients where ERP measurements were made at all three sites, then the results did not change.

Conclusion

Patients with persistent atrial fibrillation who have greater change in dispersion of refractoriness at cycle length 550 ms during the first hour following cardioversion are at increased risk of atrial fibrillation recurrence. In addition, the change in dispersion at cycle length 550 ms was the strongest predictor of the number of days to recurrence of atrial fibrillation. These findings support my hypothesis that a greater change in dispersion is associated with an increased rate of recurrence of AF following cardioversion.

In this study, a greater change in dispersion is a significant predictor of atrial fibrillation in both logistic regression and Cox regression analysis. This suggests that atrial vulnerability to AF recurrence may be due to spatial changes in refractoriness over time. Spatial changes in refractoriness over time are important in relation to AF recurrence because both greater change in dispersion and heterogeneous reverse atrial electrical remodeling were related and associated with AF recurrence. The finding that heterogeneous reverse atrial electrical remodeling is associated with increased AF recurrence also supports my hypothesis that a greater change in dispersion of refractoriness is associated with an increased risk of AF recurrence.

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