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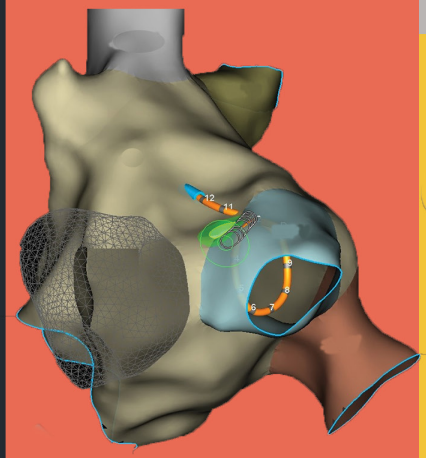

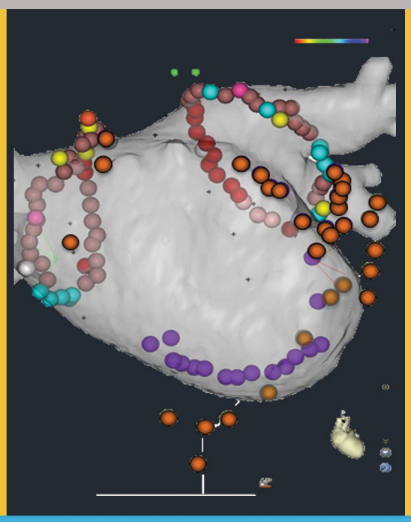

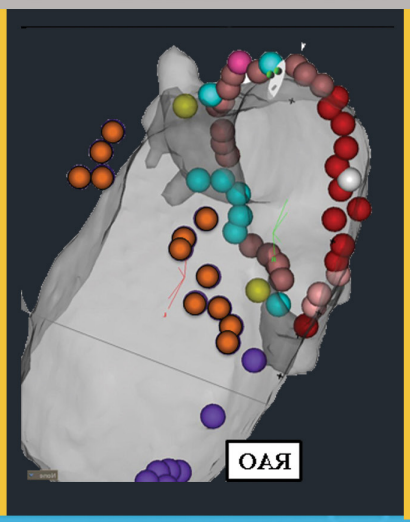

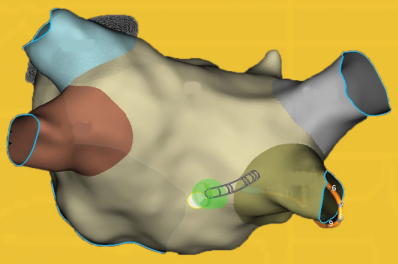

- Coronary Sinus Electrograms May Predict New-onset Atrial Fibrillation After Typical Atrial Flutter Radiofrequency ablation (CSE-AF).
- Ineffective ICD Shocks for Ventricular Fibrillation in a Patient with a Left Ventricular Assist Device: Continuous Flow during the Electrical Storm.
- Subxiphoid Hybrid Approach for Epicardial/Endocardial Ablation and LAA Exclusion in Patients with Persistent and Longstanding Atrial Fibrillation.
- Atrioventricular Nodal Catheter Ablation in Atrial Fibrillation Complicating Congestive Heart Failure

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Editorial

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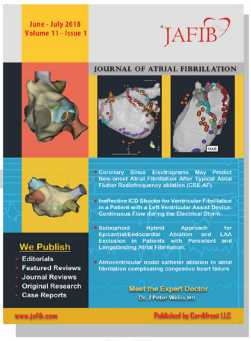

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We are Almost Through with Summer!

Dear Colleagues

Welcome to the summer issue of JAFIB. Hope everyone had a chance to enjoy the season and related travels. It has been a very interesting summer for those of us who live in North America with several hot days and unusual cold spurts in between.

In this issue of the journal we have several interesting articles presented for your reading.Pickett etal described their experience with capnography in assessing the effectiveness of the PV balloon occlusion during atrial fibrillation (AF) ablation. Their study examines the balloon-to-PV occlusion step and monitors the completeness of occlusion using capnography to measure end-tidal CO2 (ETCO2). And to determine if ETCO2 measurements can be used to quantify the amount of balloon-to-PV occlusion and to determine if acute ETCO2 parameters could predict long-term freedom from atrial fibrillation (AF). In their CAABL- CE study Srivatsa and group showed that patients with non-valvular AF, although ablation is associated with increased risk of re-hospitalization for simple AF, it was associatedwith a significant reduction in the risk of re-hospitalization for heart failure, acute coronary syndrome and severe AF.

In another small but interesting cohort of patients Mortadaetal confirmed the predictive power of atrial scar for AF recurrence in line with previously published data. There a few excellent review articles on left atrial appendage epicardial ligation system and AV node ablation in AF and heart failure. As August rolls in the annual Kansas City Heart Rhythm Symposium comes up featuring several excellent speakers. Congratulations to Prof. John Camm on receiving the KCHRS Pioneer in EP Award.

Have a great rest of the summer.
Best wishes

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Cryoballoon-to-Pulmonary Vein Occlusion Assessment via Capnography Technique: Where Does Occlusion Testing by End-Tidal CO2 Measurement "Fit" as a Predictor of Long-Term Efficacy?

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Abstract

Background: Parameters used to gauge the effectiveness of a cryoballoon lesion have been described that monitor the ablation at the time of balloon-to-pulmonary vein (PV) occlusion, during the cryoablation freeze, and at the thaw phase of the cryoablation. This study examines the balloon-to-PV occlusion step and monitors the completeness of occlusion using capnography to measure end-tidal CO_2 ($ETCO_2$). Specifically, the main objective was to determine if $ETCO_2$ measurements can be used to quantify the amount of balloon-to-PV occlusion and to determine if acute $ETCO_2$ parameters could predict long-term freedom from atrial fibrillation (AF).

Methods and Results: In a prospective study, 30 subjects were cryoballoon ablated for drug refractory symptomatic paroxysmal AF by pulmonary vein isolation method. During the balloon-to-PV occlusion and throughout the cryoablation, $ETCO_2$ measurements were recorded. The subjects were followed for a 12-month period to monitor their freedom from AF. Five subjects had a recurrence of AF outside of a 90-day blanking period but before the 12-month endpoint. Between the 25 subjects that maintained normal sinus rhythm (NSR) and the 5 subjects that had recurrent AF (rAF), there were no statistical differences in procedural parameters, including: the number of cryoablations per PV, duration of each cryoablation, balloon nadir temperature, or balloon thaw time. Additionally, there were no statistical differences in baseline $ETCO_2$ and in nadir $ETCO_2$ between the two cohorts; however, when examining Δ $ETCO_2$, the subjects in the NSR cohort had a significantly larger change compared to the rAF cohort ($P<0.001$). The largest change in $ETCO_2$ during balloon-to-PV occlusion was observed during the cryoballoon ablation of the superior PVs; however, Δ $ETCO_2$ did not solely predict long-term freedom from AF for the individual subject.

Conclusions: Δ $ETCO_2$ did tend to be larger in the NSR cohort compared to the rAF cohort; however, $ETCO_2$ monitoring was more responsive in the superior PVs and less useful in the inferior PVs. Moreover, ETCO2 monitoring could not be used as a sole indicator of long-term efficacy. Suggesting that monitoring balloon-to-PV occlusion is a necessary first in cryoballoon ablation, but other parameters must be incorporated and observed as surrogates of a circumferential and transmural lesion formation with long-term durability.

Introduction

Pulmonary vein isolation (PVI) has become a cornerstone ablation strategy in the management of patients with atrial fibrillation (AF) [1]. Additionally, the cryoballoon (Arctic Front Advance; Medtronic, Inc.) has been proven to be safe and effective when treating patients by a PVI method during catheter ablation[1]. Several key parameters have been established for long-term durable efficacy when using the cryoballoon catheter, including:[2-5] 1) before ablation is initiated, pulmonary vein (PV)-to-balloon occlusion is critical; 2) during the early phase of the freeze, the acute time-to-isolation (TTI) of a PV is important; 3) during the latter phase of the freeze, the balloon nadir temperature can be useful when TTI is unavailable; and 4) lastly, after freeze termination, the thaw time of the cryoballoon can be informative with regards to long-term durable efficacy.

Thus far, assessment techniques for PV-to-balloon occlusion have included observational descriptions or semi-quantitative methodologies[6-9]. Specifically, balloon occlusion evaluation methods have included ultrasound imaging in Doppler mode, pressure monitoring at the balloon tip, and fluoroscopy imaging of radiopaque contrast agent retention at the distal nose of the balloon[1],[6-9]. Additionally, the usage of capnography and the resulting change in end-tidal CO_2 ($ETCO_2$) has been previously described[10]. In brief, during capnogram monitoring, the PV-to-balloon occlusion creates a ventilation-perfusion mis-match that can be assessed by the decline in exhaled $ETCO_2$; however, long-term patient efficacy during follow-up has not be conducted with regard to the utility of $ETCO_2$ as a marker of PV-to-balloon occlusion. Here, we examine a cohort of patients who had $ETCO_2$ monitored during cryoballoon ablation and long-term efficacy evaluated during follow-up.

Methods

This study was a prospective single-center single-arm evaluation of 30 subjects who had a cryoballoon ablation for drug refractory symptomatic paroxysmal AF. Subjects were treated for an index ablation between June 2013 and June 2015. During the ablation, $ETCO_2$ was monitored and used to evaluate PV-to-balloon

Key Words

Atrial Fibrillation, Capnography, Catheter Ablation, Cryoablation, Cryoballoon.

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occlusion. Subjects were monitored during long-term follow-up for the recurrence of AF. The inclusion criterion was a patient scheduled to undergo an index cryoablation procedure for the treatment of paroxysmal AF using only a PVI strategy for ablation. Exclusion criteria were subjects with a patient history of diabetes mellitus or dysautonomia, age younger than 18 years or older than 90 years of age, mentally unable to give informed consent or unfit for a clinical study, and/or unable to maintain the clinical follow-up schedules through office visits and/or cardiac device monitoring. The exclusion of subjects with a clinical history of diabetes mellitus and/or dysautonomia were predefined in the study protocol because these clinical conditions can alter the baseline hemodynamics and efficacy response to catheter ablation therapy. All patients gave informed consent prior to the ablation procedure, and the study was approved by the local hospital institutional review board of St. Thomas Hospital (Nashville, TN).

Cryoballoon Ablation

The procedural techniques of cryoballoon ablation have been previously described in detail[4]. In brief, subjects held anticoagulation therapy for 24 hours before the procedure. All subjects were administered general anesthesia (propofol). Femoral venous entry was used to deliver all sheaths and catheters. A decapolar and quadripolar diagnostic catheter was placed and used in the right atrium and coronary sinus during electrophysiology recordings and atrial conduction pacing. Intravenous heparin was delivered at the time of transseptal puncture, and activated clotting time was set at a target ≥ 300 sec. Subjects underwent a cryoballoon ablation using either a 23- or 28-mm Arctic Front Advance ablation catheter which was delivered using a dedicated steerable sheath (FlexCath; Medtronic, Inc.). Balloon occlusion and freezing of the PV was conducted using an over-the-wire delivery, and high-output right phrenic nerve pacing (10-25 mA at 1,000-1,200 msec) was conducted during all right-sided PV cryoablations. Immediate freeze termination was initiated at any sign of diminished or loss of pacing capture at the diaphragm. Uninterrupted freezes were continued for a minimum of 180 sec and a maximum of 240 sec. Ablation attempts that did not achieve a balloon temperature of -40°C with 60 secs of freezing were terminated, and subsequently, the cryoballoon was repositioned for better PV occlusion. A freeze-thaw-refreeze strategy of ablation was used requiring at least two ablation attempts at each PV. Entrance and exit block testing using diagnostic catheters was conducted after a 30-minute waiting period to confirm PVI.

Capnography Measurements

The $ETCO_2$ reporting from capnography has been described, and the procedural techniques used in this study were similar to a previous description[10]. Briefly, side-stream sampling was used with the shortest possible length of tubing so that there was minimal delay between sampling and reporting of exhaled $ETCO_2$. The concentration of exhaled CO_2 gas was monitored at baseline (before a PV freeze), and subsequently, it was recorded at recurrent 30 sec intervals during the cryoablation. In quick review, $ETCO_2$ is an indicator of pulmonary blood flow which is sensitive to changes in cardiac output and/or ventilation/perfusion[10]. However, when the patient is at steady-state equilibrium during the cryoballoon ablation, the $ETCO_2$ recording is also sensitive to the PV-to-balloon occlusion. Specifically, the balloon occlusion creates a temporary circulating pulmonary blood flow deficit, and consequently, the concentration of exhaled CO_2 is reduced in response to the PV-to-balloon occlusion.

Study Design and Follow-up

The primary efficacy endpoint of the study was to determine the 1-year outcome of the cryoballoon ablation procedure in a cohort of patients who had PV-to-balloon occlusions guided and monitored with $ETCO_2$ recordings from capnography during the cryoballoon ablation procedure. The secondary endpoint of the study was to determine if any of the $ETCO_2$ recording(s) could be used to differentiate between the subjects who had recurrent AF (rAF) during follow-up and those subjects that maintained normal sinus rhythm (NSR). All subjects wore a 48-hour Holter monitor at baseline and at the end of a "landmark" 90-day blanking period. During the 90-day blanking period, recurrence of atrial arrhythmia events were allowable without penalty to the long-term efficacy endpoint to allow for cardiac healing and lesion scar formation. Complaints of palpitations led to the usage of longer periods of cardiac monitoring (7-day Holter). Subjects were followed-up for 12 months in this study with scheduled office visits at 3, 6, 9, and 12 months after the index ablation. Office visits included a review of rhythm status using ECG examination, cardiac device interrogation, review of Holter monitors, and/or evaluation of continuous loop recorders. No blinding was used in this trial.

Statistical Analyses

The change in $ETCO_2$ (denoted Δ $ETCO_2$) was calculated by subtracting the nadir $ETCO_2$ (measured during each cryoablation) from the baseline measurement of $ETCO_2$ at each PV (measured before each cryoablation). All discrete data are expressed as a count and percentage of the test cohort, and all continuous data are presented as a mean ± standard deviation. A test for normal data distribution was conducted for all continuous variables. Parametric continuous variables were tested using a t-test. A Mann-Whitney U test was used for nonparametric continuous variables. Discrete variables were tested using a Fisher's exact or Chi-square test depending on sample size. The freedom from AF calculation included a landmark 90-day blanking period in which atrial arrhythmia events were not counted as long-term efficacy failures. One-way ANOVA testing was used to test for statistical differences amongst mean values in comparisons with more than two cohorts. Statistical data analyses were conducted using SAS (version 9.4) and Minitab 17 software. Statistical significance was accepted at a two-sided $P < 0.05$.

Results

A total of 30 subjects were enrolled, treated, and monitored in this study from a pool of consecutive patients with drug refractory symptomatic paroxysmal AF (who agreed to be a part of the study and gave informed consent before the index cryoablation procedure). All patients were followed for one year after the index cryoballoon ablation by PVI method. During the 1-year follow-up, those patients who maintained sinus rhythm outside the 90-day blanking period were denoted as the NSR cohort while the rAF cohort had a recurrence of atrial arrhythmia outside the blanking period but within the 1-year follow-up period. Of the 30 subjects, 5 subjects had a recurrence of atrial arrhythmia (≥30 sec) before the 1-year follow-up period (83.3% freedom from atrial arrhythmia).

Table 1: Baseline patient characteristics. Continuous variables given as mean and standard deviation, and discrete variables given as count and percentage.

Baseline Characteristic	Total Cohort (N=30)	NSR Cohort (N=25)	rAF Cohort (N=5)	P-value*
Gender (% male)	23/30 (76.7%)	20/25 (80.0%)	3/5 (60.0%)	0.565
>Age (years)	65.7 ± 6.6	65.3 ± 7.1	67.4 ± 3.0	0.301
Left atrial size (cm)	24.1 ± 0.7	4.0 ± 0.7	4.9 ± 0.7	0.176
Left ventricular ejection fraction (%)	61.3 ± 10.9	61.2 ± 11.2	62.0 ± 9.9	0.894
History of: -Congestive heart failure	10/30 (33.3%)	8/25 (32.0%)	2/5 (40.0%)	0.999
-Coronary artery disease	6/30 (20.0%)	5/25 (20.0%)	1/5 (20.0%)	1.000
-Hypertension	24/30 (80.0%)	20/25 (80.0%)	4/5 (80.0%)	1.000

* Statistical test of significant difference between subjects in the normal sinus rhythm (NSR) cohort versus those subjects with recurrent atrial fibrillation (rAF) during the 1-year study follow-up period.

[Table 1] demonstrates the baseline clinical characteristics recorded before the index ablation. The total cohort was 77% male and had an average age of 66 years. Left atrial size was 4.1 cm (A/P) on average, and the mean left ventricular ejection fraction was 61%. In the total cohort, there was a 33% history of congestive heart failure, a 20% prevalence of coronary artery disease, and an 80% instance of hypertension. Interestingly, there were no statistical differences between the NSR and rAF cohorts regarding the recorded baseline clinical cardiovascular characteristics. Of note, the mean left atrial size of the rAF cohort was large (4.9 ± 0.7 cm) but not statistically different from the NSR cohort (4.0 ± 0.7 cm; P=0.176).

[Table 2] compares the NSR and rAF cohorts with regard to the intraprocedural parameters recorded during the cryoballoon cases. A similar percentage of the 28-mm balloons (compared to the 23-mm cryoballoons) were utilized in the NSR group compared to the rAF group with a preferential higher usage of the 28-mm cryoballoon in both cohorts. The mean number of ablations per PV were not statistically different with 2.2 ablations in the NSR group and 2.6 cryoablations in the rAF group (P=0.178). In total, there were 262 total cryoballoon lesions that were monitored during this study for intraprocedural parameters. The mean duration of each freeze was approximately 3 minutes with a mean balloon nadir temperature being achieved in 161 secs in both NSR and rAF groups. Freeze temperature at 30 sec and nadir freeze temperatures were not statistically different between the two cohorts, and thaw time from final freeze termination until +20°C exceeded 30 sec duration in both groups (as recorded by the internal cryoballoon thermocouple). Consequently, the total amount of freeze delivery in both groups (NSR versus rAF) were similar when examining the total area under the freeze curve (°C x sec).

Table 2: Comparison of acute procedural freeze parameters between subjects with normal sinus rhythm (NSR) versus subjects with recurrent atrial fibrillation (rAF).

Procedural measurement	NSR (N=25)	rAF (N=5)	P-value
Usage of 28-mm balloon	22/25 (88.0%)	4/5 (80.0%)	0.999
Number of cryoablations per PV	2.2 ± 0.6	2.6 ± 1.0	0.178
Duration of each cryoablation (sec)	172 ± 26	174 ± 43	0.788
Balloon temperature at 30 sec (°C)	-38.5 ± 10.3	-34.6 ± 5.5	0.053
Time to balloon nadir temperature (sec)	161.0 ± 31.6	160.7 ± 42.3	0.974
Balloon nadir freeze temperature (°C)	-48.6± 7.1	-48.4 ± 11.4	0.898
Balloon thaw time (sec)*	34.3 ± 14.0	38.7 18.8	0.230
Total freeze AUC (°C x sec)	-77413 ± 20033	-75111 ± 22568	0.882

* Thaw time measured from freeze termination until a +20 °C temperature is recorded by the cryoballoon internal thermocouple.

[Table 3] compares the $ETCO_2$ recordings between the NSR and rAF cohorts. The mean baseline recording of $ETCO_2$ was 41 mmHg in both cohorts. Additionally, when examining the nadir $ETCO_2$ measurement there was no statistical difference between the NSR and rAF cohorts (P=0.061). However, the Δ $ETCO_2$ measurement did show a significant difference between the NSR and rAF cohorts (P <0.001). Specifically, the NSR group had a larger change in $ETCO_2$ (between baseline and nadir recording) compared to the rAF cohort. [Figure 1] graphs this difference in Δ $ETCO_2$ in which the mean measurement for the NSR cohort is approximately 1.7X that found in the mean value of the rAF cohort.

Table 3: Comparison of end tidal CO2 (ETCO2) measurements between subjects with normal sinus rhythm (NSR) versus subjects with recurrent atrial fibrillation (rAF).

Capnogram measurement	NSR Mean ± STD	rAF Mean ± STD	P-value
Baseline ETCO2 (mmHg)	41.3 ± 9.5	40.8 ± 5.9	0.661
Nadir ETCO2 (mmHg)	34.5 ± 9.6	36.7 ± 6.6	0.061
Δ ETCO2	6.8 ± 5.0	4.1 ± 4.2	< 0.001*

* Statically significant difference

[Table 4] further evaluates the baseline and nadir $ETCO_2$ recordings specific to each PV. The difference between the mean baseline and mean nadir measurement of $ETCO_2$ was statistically different in all superior PVs (left superior (LSPV) and right superior (RSPV)) regardless of the subject's rhythm cohort membership (NSR versus rAF). This change in $ETCO_2$ over the duration of the cryoablation is depicted for the superior PVs in [Figure 2]. The left inferior PV (LIPV) did not have a statistical difference between mean $ETCO_2$ value at baseline and nadir regardless of subject cohort designation (NSR versus rAF). Interestingly, the right inferior PV (RIPV) did show a significant difference between the mean baseline

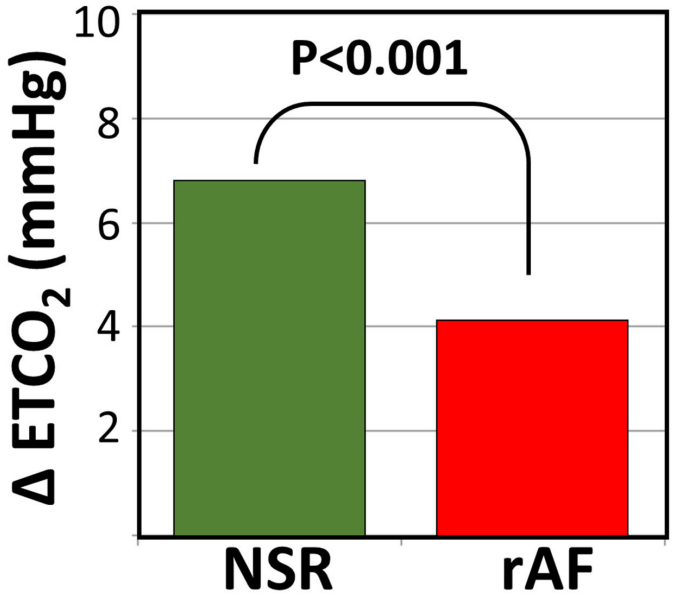

Figure 1: The change in end tidal CO2 (ETCO2) from baseline to nadir reading (Δ ETCO2) by capnography was significantly larger in the subject cohort that maintained normal sinus rhythm (NSR; green bar) throughout the 1-year follow-up period compared to the group of subjects that had recurrent atrial fibrillation (rAF; red bar).

Table 4: Comparison of end tidal CO_2 ($ETCO_2$) measurements at baseline and nadir recording when separated by each pulmonary vein (PV) and in accordance to subjects with normal sinus rhythm (NSR) versus subjects with recurrent atrial fibrillation (rAF).

Pulmonary vein and Rhythm status	Baseline ETCO2 (mmHg)	Nadir ETCO2 (mmHg)	P-value
Left Superior PV in NSR group	40.8 ± 9.9	35.7 ± 9.5	0.004*
Left Superior PV in rAF group	42.9 ± 4.6	38.2 ± 5.6	0.016*
Left Inferior PV in NSR group	41.1 ± 9.8	40.1 ± 9.6	0.568
Left Inferior PV in rAF group	41.4 ± 3.4	41.1 ± 4.7	0.827
Right Superior PV in NSR group	40.3 ± 10.4	32.1 ± 10.4	< 0.001*
Right Superior PV in rAF group	43.8 ± 3.5	35.2 ± 3.7	0.002*
Right Inferior PV in NSR group	41.5 ± 9.5	36.0 ± 10.0	0.005*
Right Inferior PV in rAF group	41.8 ± 8.1	35.3 ± 9.2	0.306

* Statically significant difference

ETCO2 measurement and the mean nadir value when examining only those subjects that remained in sinus rhythm. [Figure 3]further examines the NSR, rAF, and total population cohorts utilizing box and whisker plots. In the NSR cohort, the nadir $ETCO_2$ values tended to be lower, and the Δ $ETCO_2$ values tended to be higher when compared to the rAF cohort in both comparisons. However, a definitive "cut-off" value (to distinguish the NSR and rAF cohorts) was not apparent for either nadir $ETCO_2$ or Δ $ETCO_2$ because of the large overlap in the first and third quartiles between groups (as represented by the range of the box in each cohort).

Lastly, [Table 5] illustrates the surface area size for each PV at the orifice. There was no statistical difference in PV dimensions between the NSR and rAF cohorts when comparing the two groups by each individual PV category (LSPV, LIPV, RSPV, and RIPV) which ruled out the possibility of PV size having a confounding influence on balloon-to-PV occlusion. Also, in the total cohort, the right-sided PVs were (in general) larger in surface area at the PV orifice compared to the left-sided PVs regardless of rhythm status cohort designation (ANOVA P < 0.001). Consequently, PV orifice size was not a cause of maintenance (or non-maintenance) of sinus rhythm.

Discussion

To the best of our knowledge, this is the first study to examine the utility of capnography methods to gauge cryoballoon-to-PV occlusion and report on long-term outcomes. A previous study utilized the $ETCO_2$ recording from the capnogram to examine acute intraprocedural changes during a cryoballoon catheter ablation[10]. In congruence with this current evaluation, both studies found that the superior PVs were more responsive to balloon-to-PV occlusion when examining $ETCO_2$ (compared to the inferior PVs). The previous publication had postulated that the differential between the superior PVs and the inferior PVs may reflect the higher proportion

Table 5: Comparison of pulmonary vein orifice surface area (cm2) between subjects with normal sinus rhythm (NSR) versus subjects with recurrent atrial fibrillation (rAF).

	Pulmonary Vein Orifice Surface Area Mean ± STD (cm2)		
Pulmonary vein (PV)	NSR	rAF	P-value
Left Superior PV	2.7 ± 0.7	12.9 ± 0.6	0.527
Left Inferior PV	2.7 ± 0.7	2.3 ± 0.9	0.516
Right Superior PV	3.7 ± 1.2	3.4 ± 0.6	0.540
Right Inferior PV	3.3 ± 0.9	2.9 ± 0.6	0.328

* Statically significant difference

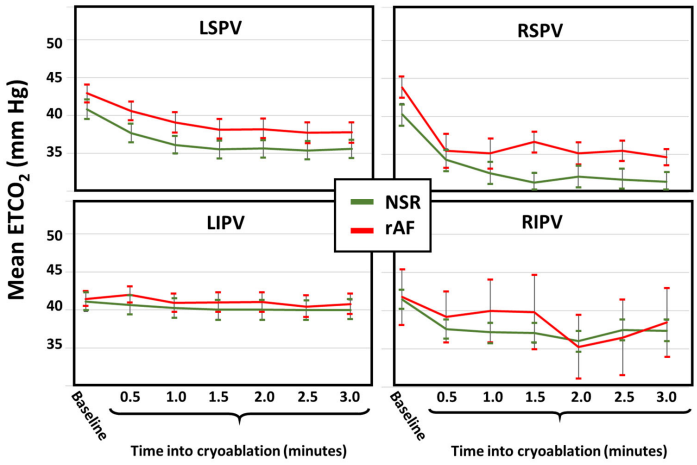

Figure 2: The change in ETCO2 over the duration of the cryoballoon ablation depicted for each pulmonary vein. The green-line graph denotes the cohort of subjects that maintained normal sinus rhythm (NSR) during the 1-year follow-up period, and the red-line graph represents the cohort of subjects that had recurrent atrial fibrillation (rAF).

of gas exchange at the upper lung lobes during general anesthesia (under volume control ventilation)[10]. Both studies agreed that $ETCO_2$ evaluation of balloon-to-PV occlusion is somewhat limited for the inferior PVs. This current study determined that the cohort of subjects that maintained long-term NSR at 1-year had a larger Δ $ETCO_2$ from baseline to nadir recording compared to the rAF cohort of subjects (when measuring the total capnogram recording at all PVs). However, other parameter of a cryoballoon ablation must also be utilized to assess the formation of a circumferential and transmural lesion. That is, the $ETCO_2$ parameter only demonstrates quality balloon-to-PV occlusion, but other parameters must be used when the delivery of freeze begins. To assess freeze propagation into the left atrial tissue, other parameters have been established (e.g., acute time-to-PVI, rate of freeze, or nadir freeze temperature)[2-4], [11-12].

Baseline Patient Characteristics and Intraprocedural

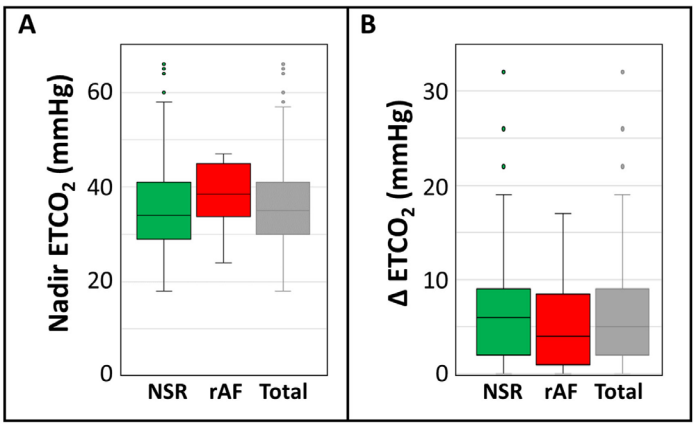

Figure 3: Box and whisker plot of subjects in three categories, including: the normal sinus rhythm (NSR) cohort in green, the recurrent atrial fibrillation (rAF) cohort in green, and the total population cohort in grey. Panel A depicts the nadir end tidal CO_2 ($ETCO_2$) reading between the three groups, and Panel B shows the change in $ETCO_2$ (Δ $ETCO_2$).

Parameters

In this current study, baseline patient cardiovascular characteristics were not different between the cohort of subjects that maintained NSR at 1-year versus those subjects that had rAF. There were no statistical differences between the NSR and rAF cohort with regard to several cardiovascular clinical characteristics. Additionally, the intraprocedural parameters were similar between both groups of subjects. These measurements included similar numbers of cryoapplications, durations of freezing, freeze nadir temperatures, and total freeze deliveries as measured by the area under the freeze curve (a measurement previously described by Aryana et al.)[11]. These data observations suggested that the difference(s) between the NSR and rAF cohorts were not a mere result of differential freeze protocols or baseline clinical patient characteristics.

Similarly, recordings of baseline and nadir $ETCO_2$ were not different between the NSR and rAF cohorts. However, the Δ $ETCO_2$ was significantly larger in the NSR cohort which was primarily driven by the differences observed at the superior PVs and to a lesser extent the RIPV. Reliable balloon-to-PV occlusion is the hallmark of the start of a robust cryoballoon ablation[4,12]. Hence, the traditional method is to examine the retrograde retention of radiopaque contrast agent under fluoroscopy imaging during balloon occlusion of the PV. The utilization of capnogram examination of $ETCO_2$ seem to be a useful adjunctive parameter during occlusion with (perhaps) some benefit to gauging more durable PVI. Importantly, PV size was not a barrier to successful occlusion testing by $ETCO_2$ recording in this study.

Clinical Implications

The current cryoballoon best practices encompasses three stages of procedural monitoring to further enhance the formation of a durable PVI[4,12]. At the start of a cryoballoon ablation, it is critical to establish balloon-to-PV occlusion[12]. During the cryoablation, time-to-acute PVI and rates of freeze can be used to assess the progression of the freeze into cardiac tissue in an attempt to monitor/ensure both circumferential and transmural lesion formation[4,12]. Lastly, the duration of thaw can be informative regarding the potential success of the freeze application[12]. In general, freeze applications with a longer thawing period are associated with durable PVI[12]. In agreement with our current study, capnography can be used as an adjunctive tool to further assess balloon-to-PV occlusion; however, other monitoring methodologies must be used to further evaluate the freeze application to ensure that the ice formation has developed both a circumferential and transmural lesion. Monitoring Δ $ETCO_2$ can be helpful to gauge balloon-to-PV contact, but other methods are needed to gauge the transmural ice formation (e.g., time-to-acute PVI).

In summary data set noted a drop in $ETCO_2$ across all superior PVs regardless of the ultimate long-term rhythm status. Hence more information is needed to observe the circumferential and transmural freezing (and lesion formation) during cryoballoon ablation,Lastly, when $ETCO_2$ did decrease the largest amount of change typically occurred in the first 60 to 90 secs from freeze initiation. Failures to achieve an $ETCO_2$ decrease in 60 secs may be used with other parameters to terminate an unsuccessful freeze attempt (e.g., slow rate of freeze and/or failure to achieve acute PVI in less than 60 secs), and instead, optioning to re-establish a better occlusion and initiate a new freeze application.

Limitations

There are several limitations with this current study. The number of subjects examined in this study is small, and hence, some of the statistical test that were near statistical significance could be been significant in a larger study cohort, including: the possibility of the NSR cohort having a colder freeze temperature at 30 secs into the ablation [Table 2] and the nadir $ETCO_2$ measurement being lower in the NSR cohort [Table 3]. While baseline patient characteristics, cardiovascular anatomies, and intraprocedural characteristics were not statistically different between the NSR and rAF cohorts, the small total population size did not allow for a statistically meaningful test of multivariable interactions. Specifically, having only five subjects in the recurrent AF cohort did not allow for robust multivariate analyses. Importantly, aAt the time of study initiation (June 2013), the literature reporting of time-to-acute PVI and other parameters of long-term success were not readily published[4,12] , and thus, these useful parameters were not recorded in our study. Consequently, we were not able to evaluate a model of long-term efficacy parameters (e.g., time-to-acute PVI) and make statistical associations that would have included measurements of $ETCO_2$. Indeed, any statistical analysismodeling would have been hampered by our small population in the current study. Lastly, this is a single-center experiment following the cryoablation results from an experienced single-operator. A larger multicenter study is needed before definitive statements can be made about the effectiveness of measuring $ETCO_2$ with regards to long-term efficacy.

Conclusion

Before a cryoballoon freeze application, the most important parameter of success is robust balloon-to-PV occlusion. The capnogram reporting of balloon-to-PV occlusion can be obtained by measuring $ETCO_2$, and a large change in $ETCO_2$ has been shown to improve long-term freedom from arrhythmia at 1-year follow-up.

Conflicts of Interest

Dr. Pickett, Ms. Owens, and Ms. Landis report no conflict of interest. Mr. Sara and Dr. Lim are employees of Medtronic.

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California Study of Ablation for Atrial Fibrillation : Re-Hospitalization for Cardiac Events (CAABL-CE)

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Abstract

Background: Catheter ablation (ABL) for non-valvular (NV) atrial fibrillation (AF) improves rhythm control. Our aim was to compare re-hospitalization for heart failure (HF), acute coronary syndrome (ACS), or recurrent AF among patients with NVAF who underwent ABL versus controls.

Methods: From the Office of Statewide Planning and Development (OSHPD) database, we identified all patients who had at least one hospitalization for AF between 2005-2013. Patients who subsequently underwent ABL were compared to controls (up to fivematched controls by age, sex and duration of AF between diagnosis and time of ABL). Cases with valve disease, open maze, other arrhythmias, or implanted cardiac devices were excluded. Pre-specified clinical outcomes including readmission for HF, ACS, severe or simple AF (severe = with HF or ACS; simple= without HF or ACS)were assessed using a weighted proportional hazard model adjusting for number of hospital admissions with AF before the ABL, calendar year of ABL, and presence of chronic comorbidities.

Results: The study population constituted 8338 cases and controls, with mean 3.5+ 1 patient-year follow up. In the ABL cohort, there was lower risk of re-hospitalizations for HF, HR=0.55(95%CI: 0.43-0.69,); ACS,HR=0.5(95%CI: 0.35-0.72,); severe AF [HR=0.86 (CI:0.74-0.99), and higher for simple AF, HR=1.25 (CI:1.18-1.33).

Conclusion: In patients with NVAF, although ABL is associated with increased risk of re-hospitalization for simple AF, ABL was associated with a significant reduction in the risk of re-hospitalization for HF, ACS and severe AF. These findingsrequireconfirmation in a prospective clinical trial.

Introduction

Atrial fibrillation (AF) is one of the most common causes of emergency department (ED) visits and hospitalizations and it is projected to affect more than 10 million Americans by 2050. The prevalence doubles with every decade of age, and morbidity is related to higher incidence of stroke, heart failure (HF) and re-hospitalization for recurrent AF episodes. HF develops in about a quarter of the patients diagnosed with AF, leading to higher mortality and there has been no decrease in this trend[1]. AF is also associated with higher risk of acute coronary syndrome (ACS), especially in women and those younger than 60 years of age. In patients presenting with ACS, associated AF increases long-term mortality compared to those without AF[2]. These findings translate to an increased health care economic burden, with an annual direct medical cost due to AF of about $3 billion more than those without AF[3].

Observational and registry data have demonstrated improved event free survival defined as non-recurrent AF > 30 seconds following ABL compared to medical management[4]. ABL is generally considered safe, but it does have certain peri-procedual complications;[5] here is an increase in HF hospitalization and recurrent arrhythmia early in the post-ABL course. However, due to advances in techniques and early recognition of these adverse effects, there has been a decreasing trend for all cause readmissions after ABL[6].

Ablation (ABL) as a first line therapy in the young is modestly cost effective with a gain of 0.06 quality-adjusted life years with an incremental cost of 3003 euros[7]. The cost effectiveness may be related to direct and indirect cost from improved quality of life and reduced hospitalizations.

Our aim was to assess the efficacy of ABL to reduce re-hospitalization for HF, ACS and recurrent AF compared to match controls in a large multi-ethnic patient population previously hospitalized for at least an episode of AF.

Methods

Data source:

California requires all non-federal hospitals in the state to report all hospitalizations and emergency department visits as well as ambulatory surgical encounters to the Office of Statewide Health Planning and Development (OSHPD). All clinical and demographic

Key Words

Atrial fibrillation Ablation, Heart Failure, Acute Coronary Syndrome

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characteristics of the individual are also recorded providing access to the co-morbidities. Since any hospitalization from any non-federal California hospital can be identified in a temporal relationship, the database is comprehensive for assessment of clinical outcomes of a procedure under investigation.

Selection of patients:

After obtaining institutional approval, clinical characteristics, demographics, hospitalization, emergency department and ambulatory surgery encounters from non-federal hospitals listed in OSHPD database were utilized for this study. ICD 9 codes were used to identify encounter diagnoses of ABL (37.34), AF (427.31), atrial flutter (AFL) (427.32), supraventricular tachycardia (SVT) (427.0), ventricular tachycardia (VT) (427.1), open surgical ablation (SA) (37.33), and pacemaker/defibrillator implant (37.80-37.87). In addition, the Elixhauser comorbidity index (Healthcare Cost and Utilization Project V3.7) was applied for 29 major co-morbidities based on ICD-9-CM codes listed as present at the time of first admission with AF[8]. The ABL group was identified as those patients with ambulatory surgery encounters for ABL between Jan 1, 2005-Dec 31, 2013 associated with principal diagnosis of AF. We excluded those with AFL, SVT, VT, SA, valvular heart disease, dementia, human immunodeficiency disease, alcohol abuse, active cancer or psychosis. All cases that had pacemaker/defibrillator implant were also excluded. Patients who had no prior encounter diagnosis of AF before ABL were excluded because they represented healthier ambulatory patients whose symptom status was unknown. The date of ABL was the study date (SDT) for this case cohort [Figure 1].

Selection of matched controls:

The control group was selected by weighted matching based on age, sex, year of onset of AF, the pattern of health-facility encounters prior to ABL and number of AF hospitalizations before the SDT. For the control group, SDT was the corresponding interval after the first encounter diagnosis of AF to the date of ABL of the matched ABL case. We reviewed sample hospitalization records to verify the accuracy of the inclusions and exclusions.

End points:

The pre-specified clinical outcomes occurring after the date of ABL included re-hospitalization for HF (principal position), ACS (principal position), and AF (principal or secondary position). Re-hospitalization for AF included those who had the diagnosis in principal or secondary position. AF was considered as severe (principal position only to avoid double counting) or simple (any position) depending on presence or absence of ICD 9 codes for ACS (410.x, 411.1, 411.8x)[9] or HF respectively during the re-hospitalization. Since ablation can cause troponin elevation, ACS was considered an outcome, if occurred > 7 days and recurrence of AF or HF was an outcome if these occurred > 90 days after the SDT. Study design is shown in [Figure 1].

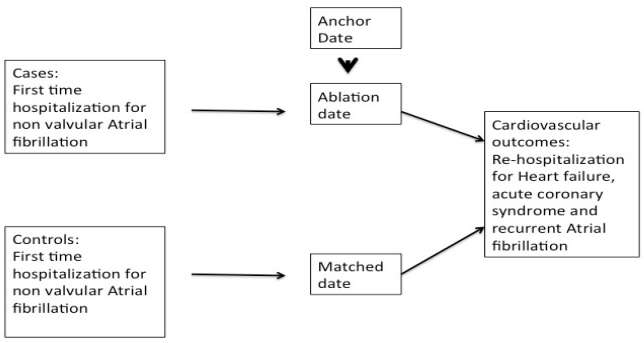

Figure 1: Study design

Statistics:

To reduce confounding effect of variables, various methods of matching have been used in observational studies. Propensity matching has been a surrogate for randomized clinical trials, however it reduces sample size of the cohorts (=power)[10]. Studies comparing the two methods (propensity score vs. simple multivariable regression) have shown no significant difference in the strength or statistical significance of associations between exposure and outcomes[11]. Since the majority of the patients with non-valvular AF (NVAF) have similar co-morbidities, regression model can be used to study the treatment effect in all patients undergoing ABL. We used weighted matching which averages multiple individuals in control group (5:1 in our study), providing 20% weight to each treated individual, providing equal number of patients in either group and reducing the variance of imbalance[10].

Outcomes in the ABL and No-ABL controls were analyzed using a weighted proportional hazard regression model with follow-up to Dec 31, 2013, adjusting for the number of prior admission with HF, and number of prior admissions with AF before ABL, calendar years, presence of specific chronic co-morbidities and demographics which were forced into the model. All co-morbidities were present at the SDT.

SAS version 9.3 was used for all statistical analyses. Continuous variables were expressed as mean + standard deviation. Categorical variables were presented as percentages. Uni-variate analysis was performed with a X^2 test for nominal variables; t test for continuous variables and Fisher's exact test was applied for outcomes fewer than 5 events per cell. A p-value < 0.05 was considered significant.

Results

The cohort comprised 8338 patients (4169 ABL and 4169 matched controls), median age 63 years, 72 % male, 79% Caucasian. Additional demographic features included 55% hypertension (HTN), 18% obesity, 17% diabetes mellitus (DM), 12% HF, 8% coronary artery disease (CAD), and 4% prior stroke. Patients were followed up for 3.5 + 1 patient-years. The control group had a significantly higher rate of co-morbidities [Table 1].

Prior to SDT, hospitalizations for AF with at least one episode of AF < 2 years were higher in ABL than control groups (81.1% vs. 77.4%, p<0.0001); the rates of hospitalization were not different (46.6% vs. 45.7%, p=ns) > 2 years prior to SDT. There was no difference between the mean number of any admission for AF before SDT between ABL and control groups (2.55 (CI 2.49-2.620 vs. 2.62 (CI 2.58-2.65), ns); however, the ABL group had more encounters

Table 1: Baseline characteristics

Characteristics		Cases (%)	Controls(%)	P value
Patient age at catheter ablation	18-34	1.9	1.8	0.4385
	35-49	13.4	12.4	
	50-64	46.2	46.4	
	65-79	35.6	36.0	
	80 or older	2.9	3.4	
Gender	Male	72.3	71.2	0.2717
Race/ethnicity	White	84.1	73.2	0.0000
Congestive heart failure		11.6	12.7	0.1502
Peripheral vascular disease		3.5	5.9	0.0000
Chronic pulmonary disease		12.9	15.9	0.0002
Diabetes		14.1	20.4	0.0000
Hypertension		58.1	51.1	0.0000
Renal failure		3.2	7.7	0.0000
Liver disease		1.2	2.4	0.0000
Coagulopathy		1.9	1.8	0.4385
Obesity		17.0	18.4	0.1178
Coronary artery disease		6.7	9.6	0.0000
Stroke/TIA		4.7	3.8	0.0528

TIA-Transient ischemic attack

for the principal diagnosis of AF < 2 years prior to the SDT (1.04 (CI: 1-1.08) vs. 0.84 (CI: 0.82-0.86), p< 0.0001)[12] [Table 2].

Regarding HF admissions before SDT, the proportion of patients in ABL and control groups, respectively, who were hospitalized for at least one episode of HF < 2 years prior to SDT was not different (9.2% vs. 10.3%, ns); there were more patients (5.6% vs. 6.8%, p=0.02) in the control group > 2 years prior to SDT, with fewer number of admissions in ABL vs. control groups within two years prior to SDT (0.23 (CI:0.2-0.25) vs. 0.33 (CI:0.31-0.35), p<0.0001). The ABL group had fewer encounters for the principal diagnosis of HF <2 years prior to SDT (0.03 (CI:0.03-0.04) vs. 0.04 (CI:0.04-0.05), p< 0.0001) [Table 2].

Clinical Outcomes:

In the ABL vs. control groups, HF hospitalization occurred in 162 vs. 309 patients within 5 years: 53 vs. 39 within 90 days and 117 vs. 287

Table 2: Episodes of Atrial fibrillation and Heart failure prior to date of ablation.

Number of episodes from index hospitalization to anchor date	Ablation (mean)	CI	Controls (mean)	CI	P value
All atrial fibrillation	2.55	(2.49,2.62)	2.62	(2.58,2.65)	0.0907
Number of encounters with Principal Diagnosis of AF within 2 years prior to ablation	1.04	(1,1.08)	0.84	(0.82,0.86)	0.0000
Number of admissions w/ CHF DX prior to ablation	0.23	(0.2,0.2)	0.33	(0.31,0.5)	0.0000

CHF- Congestive heart failure DX- Diagnosis

between 90 days – 5 years, respectively. After multivariate analysis, although there was an initial 31% increase of HF in ABL group within 90 days of SDT, (HR 1.69 (CI:1.02-2.62) p=0.02), there was a 30% reduction in ABL group within 5 years after SDT, (HR 0.7 (CI: 0.57-0.86), p=0.001). This outcome was mainly due to a 45% decrease of HF occurring 90 days after SDT in the ABL group, (HR 0.55(CI: 0.43-0.69), p<0.0001) [Table 3], [Figure 2A].

Table 3: Results comparing ablation vs. no ablation for non -valvular atrial fibrillation.

Outcomes	Cases (% person yrs.)	Controls (% person yrs.)	Hazard Ratio (CI)	P value
Heart failure (<5 years)	1.1	2.1	0.7 (0.57-0.86)	0.001
<90 days	5.3	3.8	1.69(1.02-2.62)	0.02
90 days-5 years	0.8	2.1	0.55(0.43-0.69)	<0.0001
Acute coronary syndrome (7 days- 5 years)	0.4	0.9	0.59(0.43-0.82)	0.002
7-90 days	1.3	1.5	1.26(0.56-2.84)	ns
90 days-5 years	0.3	0.8	0.5 (0.35-0.72)	<0.0001
Atrial fibrillation 90 days-5 years	17	8.6	1.77(1.63-1.93)	<0.0001
Simple AF	15.3	7	1.88(1.72-2.06)	<0.0001
Severe AF	2.8	4.1	0.86(0.74-0.99)	0.03

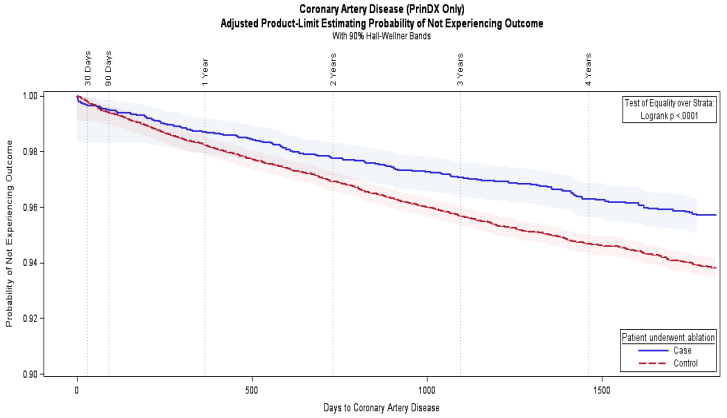

Figure 2A: Probability of not experiencing outcomes (Y axis), Days of follow up (X axis) A- Congestive heart failure

Hospitalization for ACS in ABL vs. control groups occurred in 61 vs. 131 patients, within five years: 13 vs. 15 patients < 90 days and 48 vs. 117 between 90 days – five years, respectively. After multivariate analysis, there was a 41% reduction in ABL group within 5 years after SDT (HR 0.59 (CI: 0.43-0.82), p=0.002), mainly due to a 50% decrease occurring >90 days after SDT in ABL group, (HR 0.5(CI: 0.35-0.72), p<0.0001), without a difference in ACS at <90 days ([Table 3] and [Figure 2B].

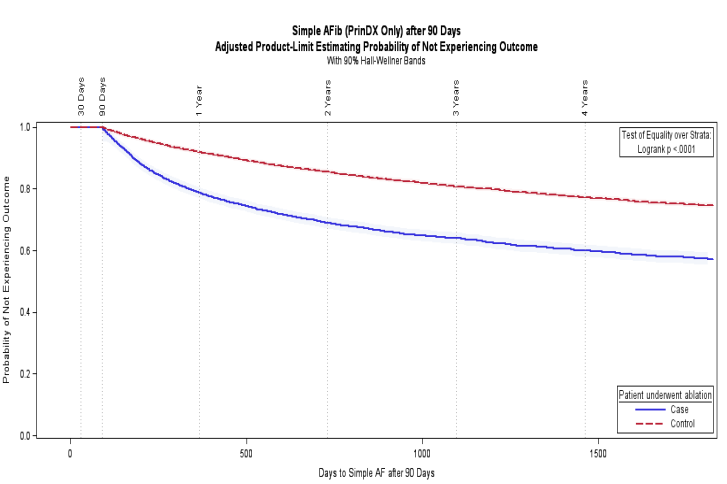

Figure 2B: Probability of not experiencing outcomes (Y axis), Days of follow up (X axis); B-Acute coronary syndrome

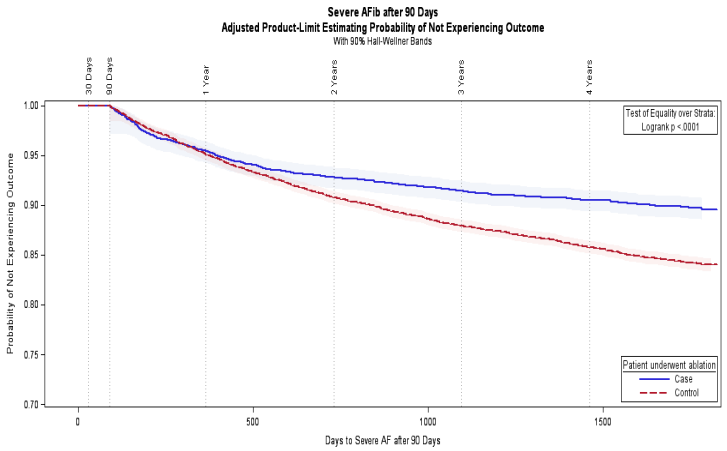

Figure 2C: **Probability of not experiencing outcomes (Y axis), Days of follow up (X axis)C- Simple Atrial fibrillation**

Regarding re-hospitalization for AF >90 days up to 5 years after SDT, there was a marginal increase in recurrence of all AF (simple and severe) in ABL vs. controls (HR 1.12 (CI: 1.05-1.19), p<0.0001), mainly attributable to simple AF (HR 1.25 (CI:1.18-1.33), p<0.0001)[Table 3], [Figure 2C]. There was a 14% reduction in severe AF (HR 0.86 (CI: 0.74-0.99), p=0.03) [Table 3], [Figure 2D] in the ABL group compared to controls.

Discussion

The major findings of this study are that re-hospitalization for HF, ACS and severe AF was reduced in patients undergoing ABL compared to the control group. However re-hospitalization for simple AF was increased in patients who had ABL. Our study group is diverse, reflecting the multi-ethnic population of California and comprised a wide age range. The majority of patients were between 50-79 years old and Caucasian males. Although California population is multi ethnic (Caucasians 44%; Hispanics 33%, Blacks 0.06%; Asians 15% and miscellaneous 7.9%), our findings are consistent with our prior report that hospitalization for AF has been higher for Caucasians, and they also have higher ABL rate[5]. As previously described, HTN was highly prevalent, with a proportion of other risk factors such as DM, CAD, HF comparable to prior investigations[13]. More

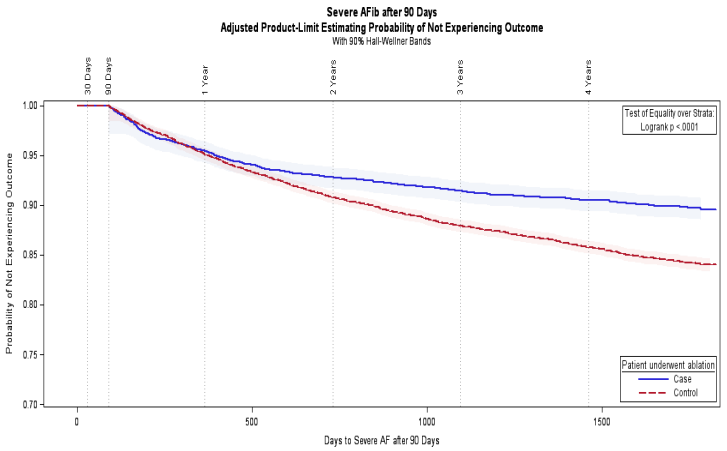

Figure 2D: **Probability of not experiencing outcomes (Y axis), Days of follow up (X axis)D-Severe Atrial fibrillation.**

patients had recent hospitalization for episodes of AF in ABL group, even though there was no difference in the number of admissions per patient. Patients had at least 2.5 hospitalizations, especially for principal diagnosis of AF before they underwent ABL; those with recent HF episodes were less likely to receive ABL, especially if HF was the principal diagnosis for that hospitalization.

A reduction in long-term HF readmissions in ABL group:

HF and AF often co-exist due to similar risk factors and co-morbidities[14]. In patients with HF, AF worsens pump function and augments mortality[15]. Additionally, HF is a cause for frequent hospitalizations in those with AF and is also associated with increased mortality[1]. Impaired atrial function in AF contributes to reduced peak oxygen consumption and cardiac output, in particular if heart rate is high;[16] Peak oxygen consumption and cardiac output are restored with return of sinus rhythm[17]. However, medical management for rhythm control has been ineffective in improving survival or reducing HF[18]. In contrast, restoration of sinus rhythm by ABL has shown improved survival and reduced HF episodes compared to non-ablated patients, in studies of AF patients with HF and reduced ejection fraction[19-21]. Preliminary results of CABANA trial indicate reduced cardiovascular hospitalization, though details of these results are not yet available. Our large study supports this finding as reflected by fewer HF hospitalizations in the ABL group. After ABL, AF episodes are known to recur at < 90 days; therefore, by convention episodes occurring after this blanking period are considered irrelevant for therapeutic failures[22]. We anticipated a higher rate of HF hospitalization at < 90 days as previously reported, possibly from peri-procedural fluid administration, inflammation and recurrent AF episodes. Our study revealed a higher rate of HF hospitalization at < 90 days; but despite this result, long term HF readmissions were 30% lower, mainly due a 45% reduction of these episodes after 90 days and through our five year follow up.

A reduction in re-hospitalization for ACS in ABL group:

CAD is a risk factor for development of AF, possibly related to atrial ischemia or the impact of left ventricular dysfunction on left atrial pressure and size[13,23]. In addition, as shown in the meta-analysis by Guo et al, patients with AF are at higher risk of MI[24]; a similar increase was noted in the atherosclerosis in the communities study (ARIC)[25]. The mechanisms for the increased risk are multifactorial, including a higher prevalence of risk factors, coronary embolism, inflammation and coronary endothelial dysfunction[26-28]. Computerized tomography has shown a higher prevalence of subclinical CAD and coronary calcification in patients with AF than in controls with sinus rhythm[29]. While there is a small risk of MI following cardioversion, the long-term decrease in hazard of ACS by maintenance of sinus rhythm is unknown. Anticoagulation reduces risk of thromboembolism, however it has not been shown to decrease ACS events[30-32]. We defined ACS based on ICD 9 codes for ST elevation MI (STEMI), non-STEMI or unstable angina. Since the objective of ABL is to create therapeutic myocardial injury, elevated myocardial markers is expected in the peri-procedural phase[33]. Therefore, in accounting for clinical outcomes, we considered only the readmissions for ACS occurring > 7 days after ABL. Our study reveals a reduction in re-hospitalization for ACS, especially >90 days after procedure during long term follow up. This could

be due to improved rhythm control or improved management of CAD. Consistent with our study, in a group of patients with AF and CAD who underwent percutaneous intervention, ABL reduced ACS compared to controls[34]. To our knowledge, ours is the first and largest study to show a reduced risk for ACS for all AF patients undergoing ABL regardless of pre-existing CAD.

An overall increase in re-hospitalization for simple AF episodes but a reduction in re-hospitalization for severe AF in the ABL group:

Regarding recurrence of AF after ABL, the majority of studies define success as non-relapse of AF > 30 seconds in duration on a monitor[22]. However despite reduced AF burden, asymptomatic episodes have been reported to be more frequent following ABL. Hospitalization for AF is a significant burden for these patients and reduction would be a beneficial clinical outcome. In a study of Medicare beneficiaries, the increased utilization of ABL has been associated with decreased 30-day re-hospitalization[35]. Our study shows an overall increase in re-hospitalization for simple AF episodes, although severe AF defined as that associated with ACS or HF was reduced in the ABL group. Simple AF recurrence could represent a low risk patient group who are very sensitive to their symptoms with a low threshold to seek medical care including ABL. Our group also represents those who underwent ablation after at least one hospitalization for AF; these patients could represent a high risk patient population. The benefits for reduced re-hospitalization in the ambulatory patients undergoing ABL without any prior hospitalization for AF cannot be assessed from our study. An increased awareness of this finding could enhance ambulatory care management of this subset of patients.

There are several important strengths within our study. The current study represents the inclusion of a multi-ethnic population, as well as the calendar period when utilization of ABL advanced most rapidly. Though we did not have access to rhythm control or anticoagulation, our results of reduction in HF and ACS provide another possible benefit from ABL for AF.

Limitations

This study is a retrospective investigation with inherent limitations of that method. However, to our knowledge this is the first and largest matched case control study of a multi-ethnic population of ABL for AF for cardiac outcomes. It depends on the accuracy of ICD 9 codes, but the validity of the data is supported by periodic audits performed for billing. We have also reviewed sample charts to ensure accuracy of exclusion and inclusion criteria. We do not have access to the actual rhythm and drugs used for treatment of the patients before and after ABL or the details of ABL strategy.

Conclusion

In this large population-based matched multivariate analysis of hospitalized patients with a diagnosis of NVAF undergoing ABL, the procedure was associated with reduced re-hospitalization for HF, ACS, and severe AF but increased readmissions for simple AF.

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Clinical Utility of Intravenous Nifekalant Injection During Radiofrequency Catheter Ablation for Persistent Atrial Fibrillation

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Abstract

Background: Radiofrequency catheter ablation (RFCA) for persistent atrial fibrillation (AF) is still challenging even in RFCA-era for AF. The aim of this study was to assess the clinical utility of nifekalant, a pure potassium channel blocker,during RFCA for persistent AF.

Methods and Results: We retrospectively enrolled 157 consecutive persistent AF patients undergoing first RFCA procedure with complex fractionated atrial electrogram (CFAE) ablation after pulmonary veins isolation and compared outcomes between patients with (NFK group: N=79) and without (No-NFK group: N=78) additional CFAE ablation using intravenous nifekalant (0.3mg/kg). Primary endpoint was 24-month atrial arrhythmia-free survival post ablation.The prevalence of AF termination was significantly higher in NFK group than No-NFK group (64.6% versus 7.7%, P<0.001). Arrhythmia-free survival, however, was not significantly different between 2 groups (61.5% versus 54.1%, P=0.63).There was no significant difference between 2 groups in the prevalence of recurrent atrial tachycardia (25.0% versus 23.5%, P=0.89). Arrhythmia-free survivalin patients with AF termination during procedure was significantly higher than those without (73.0% versus 41.0%, P=0.002; adjusted hazard ratio 0.48, 95% confidence interval 0.17-0.84, P=0.02) among NFK group,but not among No-NFK group (66.7% versus 53.2%, P=0.53).

Conclusions: Intravenous nifekalant injection during additional CFAE ablation did not improve sinus maintenance rate after RFCA procedure for AF, but AF termination by nifekalant injection could be a clinical predictor of better success rates after procedure.

Introduction

Pulmonary veins isolation (PVI) is well-established treatment for paroxysmal atrial fibrillation (AF) to eliminate the triggers of AF[1-3]. Guidelines recommended catheter ablation as second-line therapy for paroxysmal AF patients refractory to antiarrhythmic drugs (AADs) (class I) and as first-line therapy for selected symptomatic patients (class IIa)[4-5] . In contrast, catheter ablation for persistent AF is still challenging with low sinus maintenance rate after procedure, although several studies demonstrated the superiority of catheter ablation for persistent AF over conventional treatment with AADs in sinus maintenance[6,7]. Therefore, clinical utility of additional strategiesbeyond PVI to target atrial substrate such as ablation of complex fractionated atrial electrograms (CFAEs), ganglion plexus, electrical rotors and block lines have been developed, but their efficacy in addition to PVI is controversial[8-11].

AADs, especially class III AADs, increased action potential duration andsome studies had reported injection of these drugs during ablation procedure reduced CFAE sites[12-14]. We had started to use nifekalant, a pure class III AAD, during additional CFAE ablation after PVI in catheter ablation for persistent AF to detect critical CFAE sites remained even after prolongation of action potential duration by nifekalant. The aim of this study is to evaluate clinical utility of intravenous nifekalant injection during additional CFAE ablation by comparing the success rates between with and without additional CFAE ablation using intravenous nifekalantin consecutive persistent AF patients undergoing radiofrequency catheter ablation.

Key Words

Spersistentatrial Fibrillation, Radiofrequency Catheter Ablation, Complex Fractionated Atrial Electrogram, Nifekalant

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Methods

Study Population

A total of 157 consecutive persistent AF patients undergoing first radiofrequency catheter ablation with additional CFAE ablation after PVI between October 2013 and March 2016 in Kyoto university hospital were consecutively included in our analysis [Figure 1]. Intravenous injection of nifekalant during CFAE ablation was performed in 79 patients (NFK group) and the other 78 patients did not receive nifekalant during CFAE ablation (No-NFK group). The decision to use nifekalant during CFAE ablation was left to the discretion of the operators before procedure. Both groups were further subdivided into patients with or without AF termination during CFAE ablation. Persistent AF patients who showed sinus conversion during PVI and did not receive CFAE ablation were excluded in this study.

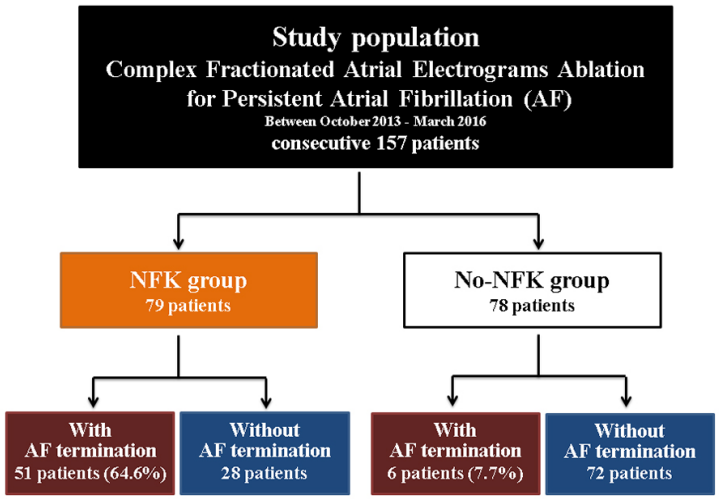


Figure 1: Study population

AF=atrial fibrillation

The present study protocol was approved by the ethics committee in Kyoto University Hospital. Written informed consent for the catheter ablation procedure and follow-up were obtained from all the patients.Follow-up information was obtained by hospital-chart review and/or telephone contact with the patient, relatives, and/or referring practitioners.

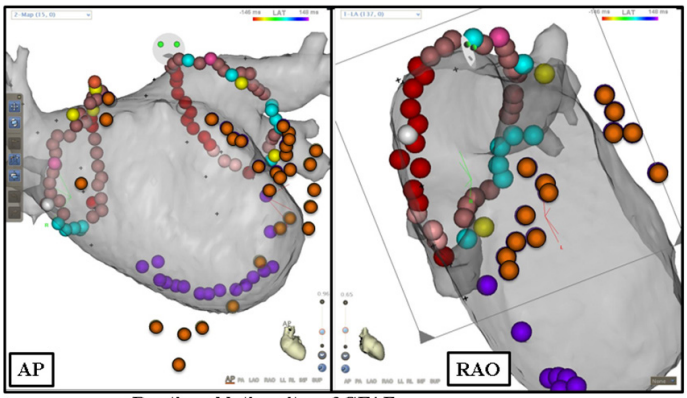
Ablation Protocol

Extensive encircling PVI was performed with a 3.5-mm tip irrigation catheter (NAVISTAR THERMOCOOL, Biosense Webster, CA, USA) and 20-pollar circular-shaped catheters (Lasso, Biosense Webster or Orbiter PV, C.R. Bard Electrophysiology, Lowell, MA, USA). After PVI, we targeted the points with CFAE, defined as intervals >120 millisecond and voltages <0.05 mV,[15] around septal and inferiormitral annulusin the direction of ostium of left atrial appendage where are common CFAE sites and have potential of inferior bilateral Ganglionated Plexi or the vein/ligament of Marshall implicated in trigger and maintenance of AF for persistent AF [Figure 2A][15-17]. In NFK group, nifekalant (0.3mg/kg) was intravenously injected after routine CFAE ablation and we targeted still remained CFAE points on both atrium, appendage or coronary sinus. Meanwhile, further CFAE ablation was not performed in no-NFK group. CFAE ablation with a power control model with a temperature setting of 40-43°C and maximal power of 25-30W was delivered for 30-40 seconds. We performed external electrical cardioversion for persistent AF even after CFAE ablationin both groups. Additional ablation for atrial tachycardia (AT) was performed only when AF converted to sustained AT. Linear left atrial ablations such as mitral isthmus line and left atrial roof line ablation were added if needed to terminate sustained AT. Tricuspid valve isthmus ablation was routinely performed regardless of the presence of typical atrial flutter.

Definitions and Outcome Measures

Persistent AF was defined as AF lasting beyond 7 days and further divided into 2 group: early-persistent AF (lasting <1 year) and long-standing AF (lasting>1 year). AF termination during procedure was defined as transition directly from AF to sinus rhythm or AT.

The primary endpoint was 24-month recurrent atrial arrhythmia-free survival with a blanking period of 3 months post ablation procedures. A 12-lead electrocardiogram was routinely measured at each clinical visit and 24-hour Holter monitoring was recommended at 3-, 6-, 12-month and yearly thereafter, especially in asymptomatic patients. Recurrent atrial arrhythmias were defined as those lasting >30 seconds or requiring repeat procedures. Clinically detected recurrent ATs were defined as regular atrial tachycardia having apparent and constant P waves in electrocardiogram. Other irregular atrial tachycardia having vague P waves was classified into recurrent AF.



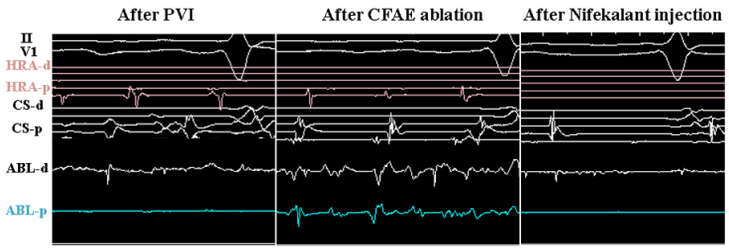


Figure 2A+2B: **A representative case of atrial fibrillation termination during procedure in NFK group.**
A) CARTOTM image with ablation points, B) intracardiac electrocardiograms
A 66-year-old man with long-standing atrial fibrillation and left ventricular dysfunction received radiofrequency catheter ablation. During procedure, we ablated sites of complex fractionated atrial electrogram (CFAE) from mitral annulus to ostium of left atrial appendage (purple points) after pulmonary veins isolation. The electrical excitation of coronary sinus was organized and, then, the cycle length was constantly prolonged by intravenously injected nifekalant (0.3mg/kg) (B). Still remained CFAE ablation, furthermore, was continued at left atrial appendage, anterior left atrium and coronary sinus (orange points). When we ablated sites of CFAEs at right atrial septum, atrial fibrillation was converted to sinus rhythm. We added tricuspid valve isthmus ablation and finished procedure. Sinus rhythm has been maintained for 906 days and left ventricular function is recovered.

AP=antero-posterior view, d=distal, CFAE=complex fractionated atrial electrogram, CS=coronary sinus, HRA=high right atrium, p=proximal, RAO=right anterior oblique view

Statistical analysis

Categorical variables were presented as number and percentage and were compared with the chi-square test when appropriate; otherwise, we used Fisher's exact test. Continuous variables were presented as mean and standard deviation, and were compared using the Student's t-test. We used the Kaplan-Meier method to estimate 24-month atrial arrhythmia-free rate, and assessed the difference with the log-rank test. The impact of AF termination on recurrent atrial arrhythmia after procedure in NFK group was evaluated by multivariable analysis using the Cox proportional hazard model with the following patients and procedural variables: long-standing AF, female gender, presence of diabetes, and left atrial diameter beyond 50mm in transthoracic echocardiography.Statistical analyses were performed using JMP 10 (SAS Institute Inc, Cary, NC) software. All the analyses were two-tailed, and P value <0.05 was considered statistically significant.

Results

Baseline characteristics

Mean age of the present study population was 66 years and 77% of patients were male [Table 1]. CHADS2 and CHA2DS2-VASc score were relatively low (1.8 and 2.9, respectively). The prevalence of long-standing AF was 40%. Left atrium was dilated (46mm) and the prevalence of severely dilated left atrium beyond 50mm was 21%.The baseline characteristics between NFK and Non-NFK group were not significantly different, except for the prevalence of hypertension. The prevalence of AF termination during procedure was significantly higher in NFK group than No-NFK group (64.6% versus 7.7%, P<0.001). A representative case of AF termination in NFK group was described in [Figure 2B]. Procedure time for CFAE ablation was significantly higher and relatively more additional block line ablation was required in NFK group than No-NFK group, although total procedure time was not significantly different between 2 groups (204min versus 197min, P=0.20).

Table 3: Demonstrates the procedural data

	All N=157	NFK group N=79	No-NFK group N=78	P value
Age (years)	65.7±9.0	65.9±10.2	65.4±7.6	0.72
Age ≥75 years	23 (14.7%)	16 (20.3%)	7(11.4%)	0.04
Female gender	36 (22.9%)	19 (24.1%)	17(21.8%)	0.74
History of heart failure	25 (15.9%)	16 (20.3%)	9 (11.5%)	0.13
Hypertension	68 (43.3%)	38 (48.1%)	51 (65.4%)	0.03
Diabetes	26 (16.6%)	15 (19.0%)	11 (14.1%)	0.41
Ischemic Stroke	13 (8.3%)	6 (7.6%)	7 (9.0%)	0.75
Vascular disease	15 (9.6%)	10 (12.7%)	5 (6.4%)	0.18
CHA2DS2 score	1.8±1.4	1.7±1.4	1.9±1.4	0.50
CHA2DS2-VASc score	2.9±1.7	2.8±1.8	2.9±1.6	0.75
Long-standing atrial fibrillation	62 (39.5%)	30 (38.0%)	32 (41.0%)	0.70
Echocardiography				
Left ventricular ejection fraction (%)	60.5±13.3	59.0±14.7	61.9±11.6	0.18
Left atrial diameter (mm)	45.7±6.0	46.1±6.3	45.2±5.8	0.34
>50 mm	33 (21.2%)	19 (24.4%)	14 (18.0%)	0.33
Procedure characteristics				
Total procedure time (minutes)	201±38	204±41	197±35	0.20
Time for CFAE ablation (minutes)	46.1±6.3	55±24	42±21	<0.001
Superior vena cava isolation	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Block line ablation	15 (9.6%)	11 (13.9%)	4 (5.1%)	0.06
AF termination	57 (36.3%)	51 (64.6%)	6 (7.7%)	<0.001

Categorical variables are presented as number (percentage). Continuous variables are presented as mean ± SD. CFAE= complex fractionated atrial electrogram.

Table 2: Independent risk factors for recurrent atrial tachyarrhythmia in NFK group

	Univariate			Multivariable		
Variables	HR	95% CI	P value	HR	95% CI	P value
Female gender	1.59	0.68-3.41	0.27	2.05	0.76-5.15	0.15
Diabetes	0.42	0.10-1.21	0.12	1.05	0.15-1.98	0.48
Left atrial diameter >50 mm	2.30	1.01-4.97	0.047	2.53	0.03	0.48
AF termination	0.33	0.15-0.69	0.004	0.38	0.17-0.84	0.02
Long-standing AF	1.94	0.92-4.11	0.08	2.18	0.91-5.26	0.08

AF=atrial fibrillation, CI=confidence interval, and HR=hazard ratio.

In NFK group, total procedure time was significantly shorter in patients with AF termination during procedure despite the high prevalence of additional block line ablation than those without (Supplementary [Table 1]). There was no significant difference in any of baseline and procedure characteristics between patients with and without AF termination during procedure in No-NFK groups (Supplementary [Table 2]).

Recurrent atrial arrhythmia with or without nifekekalant

Mean follow-up duration was 686±296 days. Recurrent atrial arrhythmia-free survival rateafter the first procedure in NFK group was 73.0% at 6-month, 66.1% at 12-month, 61.5% at 18-month, and 61.5% at 24-month, which was equivalent with that in No-NFK group: 74.3% at 6-month, 63.9% at 12-month, 59.6% at 18-month, and 54.1% at 24-month (P=0.63) [Figure 3A]. 7 out of 28 patients (25.0%) with recurrent atrial arrhythmia in NFK group and 8 out of 34 patients (23.5%) in No-NFK group were documented ATs (P=0.89).The arrhythmia-free survival rate after the last procedure was also not significantly different between NFK group and No-NFK group (75.9% versus 75.6% at 24 months, P=0.83) [Figure

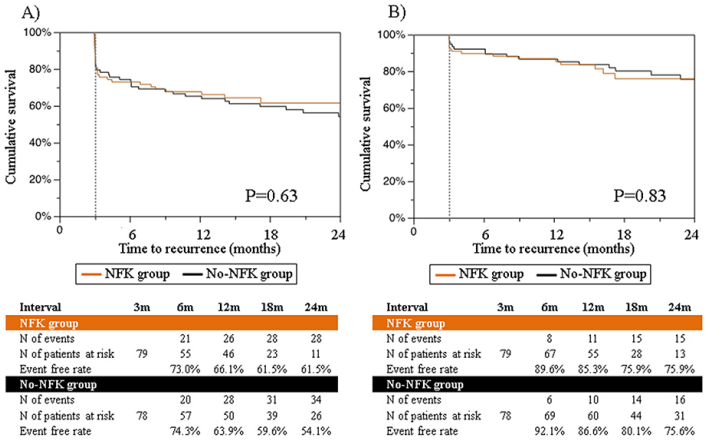
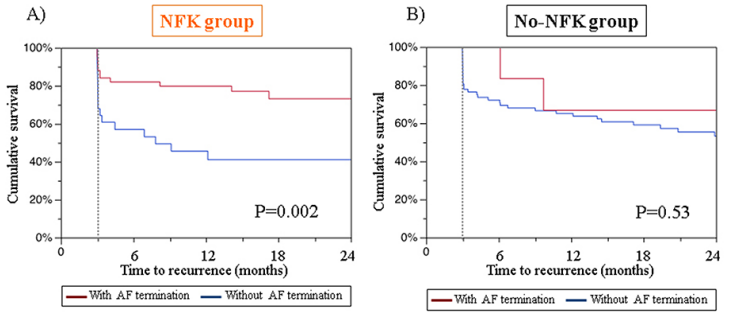


Figure 3(A,B): Recurrent arrhythmia-free survival between NFK group and No-NFK group A) after the first procedure ,and B) after the last procedure

3B]. Furthermore, the comparable arrhythmia-free rates between NFK group and No-NFK group werepreserved in both patients with early-persistent and long-standing AF (Supplementary [Figure 1]).

AF termination during procedure

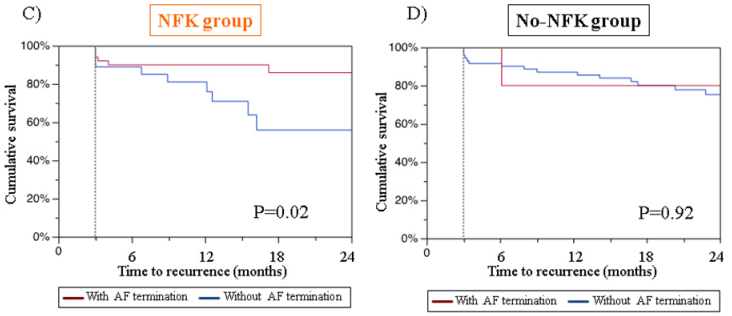
Among 79 patients in NFK group, recurrent atrial arrhythmia-free survival rate after the first procedure in patients with AF termination during procedure was 81.9% at 6-month, 79.8% at 12-month, 73.0% at 18-month, and 73.0% at 24-month, which was significantly higher than those without: 56.9% at 6-month, 41.0% at 12-month, 41.0% at 18-month, and 41.0% at 24-month (P=0.002) (Figure4-A). AF termination during procedure, furthermore, was a significant predictor for arrhythmia-free success after procedure in multivariable analysis among NFK group (hazard ratio 0.48, 95% confidence interval 0.17-0.84, P=0.02) [Table 2]. The prevalence of recurrent ATs was significantly higher in patients with AF termination than those without (50.0% versus 6.3%, P=0.01). Among 78 patients in



Interval	3m	6m	12m	18m	24m
With AF termination					
N of events		9	10	12	12
N of patients at risk	51	40	36	19	10
Event free rate		81.9%	79.8%	73.0%	73.0%
Without AF termination					
N of events		12	16	16	16
N of patients at risk	28	15	10	5	1
Event free rate		56.9%	41.0%	41.0%	41.0%

Interval	3m	6m	12m	18m	24m
With AF termination					
N of events		0	2	2	2
N of patients at risk	6	6	4	4	3
Event free rate		100%	66.7%	66.7%	66.7%
Without AF termination					
N of events		20	26	29	32
N of patients at risk	72	51	46	36	24
Event free rate		72.1%	63.7%	59.1%	53.2%

Figure 4(A,B): **Recurrent arrhythmia-free survival after the first procedure between patients with and without AF termination A) in NFK group, B) in No-NFK group**



Interval	3m	6m	12m	18m	24m
With AF termination					
N of events		5	5	6	6
N of patients at risk	51	44	39	22	12
Event free rate		90.0%	90.0%	85.9%	85.9%
Without AF termination					
N of events		3	6	9	9
N of patients at risk	28	23	16	7	2
Event free rate		88.9%	75.9%	55.8%	55.8%

Interval	3m	6m	12m	18m	24m
With AF termination					
N of events		0	1	1	1
N of patients at risk	6	6	5	4	3
Event free rate		100%	80.0%	80.0%	80.0%
Without AF termination					
N of events		6	9	13	15
N of patients at risk	72	64	56	41	29
Event free rate		91.5%	87.1%	80.1%	75.3%

Figure 4(C,D): **Recurrent arrhythmia-free survival after the first procedure between patients with and without AF termination A) in NFK group, B) in No-NFK group**

No-NFK group, in contrast, 24-month arrhythmia-free rate after the first procedure was not significantly different between patients with and without AF termination during procedure (66.7% versus 53.2%, P=0.53) [Figure 4A,Figure 4B]. The prevalence of recurrent ATs was twice, but not significantly higher in patients with AF termination than those without (50.0% versus 21.9%, P=0.42). Recurrent atrial arrhythmia-free survival rate after the last procedure was also significantly different between patients with and without AF termination in NFK group (85.9% versus 55.8%, P=0.02), but not in No-NFK group (80.8% versus 75.3%, P=0.92) [Figure 4C,Figure 4D]. The better arrhythmia-free rates in patients with AF termination were more pronounced in long-standing AF (Supplementary [Figure 2]).

Discussion

This study demonstrated clinical utility of intravenous nifekalant injection during CFAE ablation in consecutive 157 patients undergoing catheter ablation for persistent AF patients. We found that the strategy did not improve sinus maintenance rate after procedure despite further CFAE ablation on PVI, although AF termination during CFAE ablation with nifekalant was associated with favorable outcomes after procedure.

CFAEs were described by K. Nademanee, et al in 2004 and several previous studies showed that substrate modification targeted to CFAEs improved arrhythmia-free rate after catheter ablation procedure[15,18,19]. Conversely, broad ablation of all CFAEs could result in greater tissue destruction during catheter ablation for persistent AF and induce complex ATs after procedure[8,20,21].STAR AF II trial, a recent randomized trial comparing three approaches to substrate ablation for persistent AF, showed no efficacy of CFAE and left atrial linear ablations[9] .Y. Lin et al., however, reported limited CFAE ablation, targeted areas of mean CFAE interval <60 milliseconds, improved arrhythmia-free survival after procedure compared with ablation of extensive CFAEs, defined as CFAE interval <120 milliseconds[22]. In substrate modification, we should detect critical contributor on maintenance of AF and avoid unnecessary tissue destruction so as not to induce complex ATs.

In the present study, weassessed the utility of further CFAE ablation with nifekalant. Nifekalant, developed in Japan, increases effective refractory period via blockade of cardiac delayed rectifier of potassium current and is called a pure class III AAD like ibutilide abroad because they are distinguished from most other class III AAD blocking sodium and calcium current as well as potassium current[12-14,23].These drugs are usually used for ventricular arrhythmia, but have potential to convert current-onset atrial arrhythmia to sinus rhythm by increasing effective refractory period[24,25]. Regarding radiofrequency catheter ablation for AF, several small studies showed injection of these drugs after PVI provided certain rate of sinus conversion during procedure even in persistent AF or reduced areas of CFAE potential during persistent AF[14,26-28].Therefore, we believed still electrically fragmented sites where satisfied CFAE criteria even after increased effective refractory period by injection of these drugs might be critical contributors on maintenance of AF and CFAE ablation targeted these critical sites could reduce AF recurrence without increased ATs. CFAE ablation with nifekalant, however, did not improve clinical outcomes after procedure in this study, consistent with previous studies of CFAE ablation after injection of ibutilide or nifekalant[27,28].Further studies would be desired to validate the utility of substrate ablation, including CFAE, electrophysiological rotor, and low voltage ablation, in combination with these drugs.

Previous studies had reported the favorable outcomes after AF

termination during stepwise ablation with CFAE ablation, although Kochhauser, et al. recently reported poor correlation between AF termination and favorable prognosis[8,29-30]. In the present study, meanwhile, AF termination was increased by nifekalant injection and predicted favorable prognosis after procedure in NFK group. The prevalence of ATs among recurrent atrial tachyarrhythmias was increased in patients with AF termination but the incidence of recurrent atrial tachyarrhythmias including AF and ATs was decreased in total. Furthermore, the favorable impact of AF termination by nifekalant was preserved even after repeat procedures. Therefore, AF termination by nifekalant might prove proper substrate modificationand might indicate us the timing we should stop further substrate modification. The stepwise approach requires drastic ablation until AF is terminated, while nifekalant injection during substrate ablation could be a clinical indicator to detect patients with favorable outcomes after procedure withminimum tissue destruction by reducing unnecessary ablation.

Study Limitations

There are several limitations that should be considered. First and most importantly, our study population, especially patients with AF termination in No-NFK group, was small and we might underestimate each impact on clinical success. Further study is needed to establish the utility of nifekalant during catheter ablation for persistent AF. Second, this study was a non-randomized control trial and whether or not operators use nifekalant left to the discretion of them. However, most patients were ablated by one main operator and most baseline characteristics were, fortunately, not significantly different between NFK and Non-NFK group. Finally, generalizing our results to populations outside Japan should be done with caution because study population was all Japanese and effect of nifekalant has been proven mainly for Japanese.

Conclusions

Intravenous nifekalant injection during additional CFAE ablation did not improve sinus maintenance rate after RFCA procedure for AF, but AF termination by nifekalant injection could be a clinical predictor of better outcomes after procedure.

Conflicts of interest

None

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Prognostic Value of Atrial Fibrillation Inducibility in Patients Without History of Clinical Atrial Fibrillation

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Abstract

Purpose: During invasive electrophysiological studies (EPS), atrial fibrillation (AF) can be induced in patients without a history of AF. However, the prognostic value is not well evaluated in this population. Our aim was to investigate whether AF inducibility in those patients is associated with future clinical episodes of AF; whether non-inducibility is predictive of freedom from new-onset AF and finally, to examine clinical factors associated with inducibility.

Methods: Medical records from patients undergoing EPS between the years 2011 and 2014 were analysed retrospectively with 62 patients matching our inclusion criteria. Patients were divided into subgroups according to their inducibility status and underwent follow-up. Patients were assessed by a structured telephone interview, data from the further treating physicians and ECG recordings.

Results: AF was inducible in 19 patients („induction group") and not inducible in the remaining 43 („control group"). Inducibility was associated with a higher age (p=0.002), lower GFR (p=0.002), higher CHAD2S2-VASc score (p=0.004) and diagnosis of mitral (p=0.014), tricuspid (p=0.017) and pulmonary (p=0.026) valve insufficiency. Three months after EPS, 89.5% of all inducible patients were free of diagnosed AF, in contrast to 100% of those without inducibility (p=0.031). At three years, no significant difference was left (p=0.162).

Conclusion: AF inducibility was found more often in an older population with cardiac comorbidities. While inducibility was associated with an increased rate of diagnosed new-onset clinical AF in the months after testing, non-inducibility seemed to be associated with freedom from AF at least in the short to medium term. However, there was no significant difference in the long term follow-up.

Introduction

Within the last decade, the burden of atrial fibrillation (AF) has almost doubled in Europe, affecting between 1.9% and 2.9% of the general population and, according to estimates, more than 33.5 million people worldwide in the year 2010[1,2]. Data derived from the Framingham Heart Study even suggest a lifetime risk of 1 in 6 patients without structural heart disease for the development of atrial fibrillation or atrial flutter[3]. Undetected and –treated, AF bears a significant risk for the development of tachycardiomyopathy and stroke[4,5]. It is well established that prolonged episodes of atrial fibrillation can induce various pathways that stabilize and fuel the disease[6]. According to a widely accepted model, paroxysmal atrial fibrillation is thought to be the result of rapid triggering by ectopic foci or a single re-entry mechanism in the area around the pulmonary veins, while the more persistent or permanent forms are based on multiple functional or structural re-entry mechanisms, partly caused by remodelling processes provoked by the arrhythmia itself (i.e. altered ion channel functions that lead to a shortening of the atrial refractory time and thus to the further stabilization of the condition) and by structural remodelling of the atria with development of atrial fibrosis[5,7,8]. Those findings are reflected in current treatment guidelines, i.e. the use of RAS inhibitors and other medications for the prevention of further proliferation of proarrhythmogenic fibrotic tissue, also known as upstream therapy[9], as they have also sparked inventions in the field of interventional electrophysiology, with Haïssaguerre et al being the first to demonstrate that radio-frequency ablation of the tissue around the pulmonary veins could cure the disease at least in certain patients[10]. Yet, there is still a good deal of unsettled questions left, not only regarding different modes of therapy but also regarding novel strategies for the detection of atrial fibrillation. Identifying risk factors that predispose patients to develop AF might help to reduce subsequent disabilities.

During invasive electrophysiological studies (EPS), AF can be induced via high rate atrial burst pacing, sometimes also in patients without a history of the disease. However, the prognostic value of this test is largely unknown. In this study, we hypothesised that inducibility of AF during EPS is associated with a higher risk to develop clinical AF and that noninducibility is a valid predictor of freedom from new-onset atrial fibrillation.

Key Words

Atrial Fibrillation, Inducibility, Follow-up, Prognostic Value.

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Methods

Patient Population

Medical records from patients that underwent EPS from 2011 to 2014 at the University hospital of Tuebingen, Germany were screened for attempted AF induction by high rate atrial burst pacing and divided into two group according to their inducibility status. Indications for EPS (multiple nominations possible) in the final cohort were: suspected paroxysmal supraventricular or ventricular tachycardia (42.0%), risk stratification in patients with cardiomyopathy or reduced left ventricular ejection fraction (40.4%), unclear syncope (33.9%) and others (16.0%). Patients were excluded if a structured interview via telephone was not feasible. Other exclusion criteria were: previous episodes of AF, atrial flutter or atrial tachycardia; congenital heart defects with corrective surgery, history of valve surgery or other major heart operations; cryptogenic stroke; history of catheter ablation in the atria other than ablation due to AVRT/AVNRT; successful induction after the previous administration of a beta-adrenergic agent (i.e. Orciprenalin).

All patients were legally competent and gave their informed consent. The study was approved by the local ethics commission. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

AF Induction

As the study was designed retrospective, the setting and performance of the EPS was dependant on the indication that lead to the examination and also on the responsible physician. However, according to the operating protocol of the cardiological department of Tuebingen University Hospital, patients are usually called to stop their medication before undergoing EPS if treated with beta blocking agents or other drugs potentially interacting with the electrical vulnerability of the heart within at least 24-48 hours before testing. For AF induction, a decapolar CS catheter, spacing 2-5-2 mm, is then placed into the coronary vein sinus, the proximal pair positioned at the CS ostium enabling single site pacing. Burst stimulation is usually performed at double pacing threshold or at least 5 mA and 3 ms pulse width, 3 seconds per burst with a pause of 3000 ms between, starting from CL 300 ms and decrementing by 10 ms down to 200 ms or the shortest cycle length that resulted in a 1:1 atrial capture or until AF is induced within that range.

According to literature, fast and irregular atrial activation >2 seconds was defined as non-sustained AF and inducible episodes > 30 seconds as sustained AF[11,12]. Patients get cardioverted after more than 10 minutes of sustained AF. An example of successful AF induction is shown in [Figure 1].

Follow-up

Patients were contacted and questioned in a structured telephone interview about their current health status, recent (cardiological) examinations or tests, newly diagnosed heart diseases with a special focus on heart rhythm disorders, newly started medications with a special focus on antiarrhythmic and anticoagulant drugs and about having experienced certain symptoms of TIA or stroke. The patients were briefed to consult a healthcare provider if experiencing symptoms pointing to arrhythmias and were asked for permission to contact the further treating physicians (primary care and private-practice cardiologists) later on for further information regarding their post-EPS state of health. If available, data from the emergency department, the cardiological outpatient department and inpatient ward that were gained in the meantime after EPS were also analysed. The mean follow-up time was 32.5 months in the induction group and 26.7 months in the control group, showing no statistically relevant difference ($p = 0.134$). 52.6% of the patients in the induction group and 48.8% of the patients in the control group received one or more examinations via Holter monitoring or ICD/ pacemaker/ event recorder interrogation and further 42.1% of the patients in the induction group and 37.2% in the control group had at least one (or more) 12 channel ECGs performed on them during the course of follow-up.

Statistical Analysis

Statistical analysis was performed using the Chi-Squared test or the Fisher's exact test. The categorical variables were treated as binary. For inter-group comparisons, testing for Gaussian distribution was performed using the Shapiro-Wilk test. Parametric data were then analysed using mean value, standard distribution, the Levene test and t-test, non-parametric data were analysed using the median value and the Mann-Whitney-U test. A Kaplan-Meier analysis was performed to estimate the AF-free survival rate in both groups, with a log-rank test used to test for possible statistically significant differences. Statistical significance was defined as $p < 0.05$.

Results

Induction of Atrial Fibrillation During EPS

62 patients matched our inclusion criteria. Of those, 19 were defined as AF inducible ("induction group", 18/19 respectively 94.7% with sustained AF, 1/19 with non-sustained AF) and 43 as AF non-inducible ("control group"). One member of the induction group died during the course of follow-up from a non-cardiac cause (cancer of unknown primary).

The clinical characteristics of our patient populations are given in [Table 1]. The induction group consisted of 8 male and 11 female patients (42.1% vs. 57.9%). In the control group, 28 patients were male and 15 were female (65.1% vs. 34.9%). The differences were not statistically significant (p=0.09). The members of the induction group were significantly older than their counterparts (median age 69 years vs. 48 years, p=0.002). No differences were observed in the patients' body-mass indexes (induction group 27.7 kg/m^2 with SD

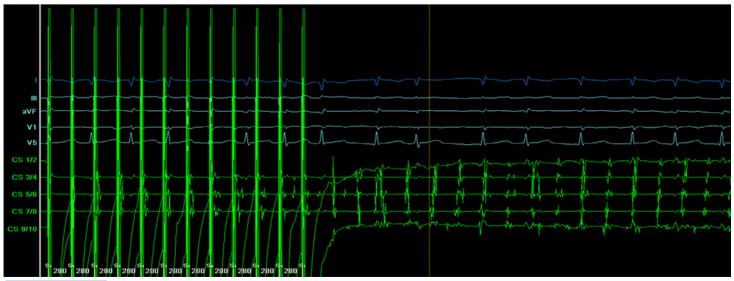

Figure 1: Example of AF induction. High rate atrial burst (CL 280ms) pacing leads to atrial instability with a subsequent development of atrial fibrillation.

Table 1: Baseline data and clinical assessment stratified by inducibility status

	Positive AF Inducibility	Negative AF Inducibility	P-value
Sex			
Total Number	19	43	
Male	42.1% (8/19)	65.1% (28/43)	p=0.090
Female	57.9% (11/19)	34.9% (15/43)	
Age			
Median Age (years)	69	48	p=0.002
Interval 1 (< 29 years)	0.0% (0/ 19)	27.9% (12/43)	
Interval 2 (30-59 years)	31.6% (6/ 19)	53.5% (23/43)	
Interval 3 (60-99 years)	68.4% (13/19)	18.6% (8/43)	
Body-Mass Index			
BMI Mean Value (in kg/m²)	27.7	26.7	p=0.541
Standard Deviation	5.0	6.2	
Cardiovascular Risk Factors			
Hypertension	63.2% (12/19)	39.5% (17/43)	p=0.086
Dyslipidemia	47.4% (9/19)	23.3% (10/43)	p=0.058
Nicotine Abuse	26.3% (5/19)	14.0% (6/43)	p=0.28
Diabetes Mellitus	15.8% (3/19)	11.6% (5/43)	p=0.692
Fam. Predisposition	31.6% (6/19)	18.6% (8/43)	p=0.327
Median Count	2	1	p=0.054
Comorbidities			
CAD	42.1% (8/19)	23.3% (10/43)	p=0.132
CMP	10.5% (2/19)	23.3% (10/43)	p=0.313
LBBB	21.1% (4/19)	11.6% (5/43)	p=0.437
Myocarditis	5.3% (1/19)	7.0% (3/43)	p=1.000
Myocardial Infarction	15.8% (3/19)	14.0% (6/43)	p=1.000
SVT	21.1% (4/19)	14.0% (6/43)	p=0.479
VT	10.5% (2/19)	16.3% (7/43)	p=0.709
Syncope	42.1% (8/19)	37.2% (16/43)	p=0.715
Hyperthyreoid Disorder	21.1% (4/19)	7.0% (3/43)	p=0.187
Hypothyreoid Disorder	10.5% (2/19)	7.0% (3/43)	p=0.638
Renal Insufficiency	0.0% (0/19)	4.7% (2/43)	p=1.000
Depression	10.5% (2/19)	4.7% (2/43)	p=0.580
Sleep Apnoea Syndrom	5.3% (1/19)	2.3% (1/43)	p=0.522
Laboratory Results			
Potassium Mean Value (in mmol/l)	4.2 (SD 0.4)	4.3 (SD 0,4)	p=0.456
GFR Mean Value (in ml/min/1,73m²)	80.0 (SD 14.0)	101.0 (SD25.0)	p=0.002
Creatinine Median (in mg/dl)	0.9	0.8	p=0.346
TSH Median (in mU/l)	1.2	1.4	p=0.768
Echocardiographic Data			
Median LVEF	60.0%	60.0%	p=0.684
ED Mean Value (in mm)	48.3	52.0	p=0.324
Standard Deviation	9.5	9.2	
ES Median (in mm)	35.0	32.5	p=0.603
Septal Thickness Median (in mm)	12.0	12.0	p=0.921
Atrium Parasternal Mean Range (in mm)	37.9	39.1	p=0.649
Standard Deviation	6.1	6.8	
Atrium Apical Mean Range (in mm)	20.7	20.8	p=0.977
Standard Deviation	6.1	5.6	
Mitral Insufficiency	69.2% (9/13)	24.1% (7/29)	p=0.014
Aortic Insufficiency	33.3% (4/12)	13.3% (4/30)	p=0.195
Pulmonary Insufficiency	50.0% (4/8)	8.7% (2/23)	p=0.026
Tricuspid Insufficiency	75.0% (9/12)	32.3% (10/31)	p=0.017
CHAD2S2-VASc Score			
CHAD2S2-VASc Score Median	2	1	p=0.004
CHAD2S2-VASc 0	10.5% (2/19)	41.9% (18/43)	
CHAD2S2-VASc 1	10.5% (2/19)	16.3% (7/43)	
CHAD2S2-VASc >=2	78.9% (15/19)	41.9% (18/43)	

5.0 vs. control group 26.7 kg/m² with SD 6.2, p=0.541).

Remarkably, atrial fibrillation was not inducible in any patient younger than 30 years. The age distribution in each group is demonstrated in [Figure 2].

Clinical Assessment - Risk Factors, Comorbidities, Laboratory Results and Echocardiographic Data

No statistically significant differences between both groups were found regarding the documented patients' cardiac risk factors (hypertension, dyslipidemia, nicotine abuse, diabetes mellitus and familiar predisposition) and the pre-diagnosed cardiac and medical comorbidities in the study population (CAD, cardiomyopathy, left bundle branch block, myocarditis, myocardial infarction, supraventricular or ventricular tachycardia, syncope, thyroid disorders, renal insufficiency, depression and sleep apnoea) at the time of EPS. Although the glomerular filtration rate (MDRD – GFR) was significantly lower in in the induction group (mean value 80.0 ml/min/1.73m² vs. 101.0 ml/min/1.73m², p=0.002), there was no significant difference regarding the patients' potassium, creatinine and TSH levels. However, statistical significance was found regarding mitral, tricuspid and pulmonary valve insufficiencies of any degree. Mitral valve insufficiency was found to be present in 69.2% of the induction group and in 24.1% of the control group (p=0.014), tricuspid valve insufficiency was found in 75.0% of the induction group vs. 32.3% of the control group (p=0.017) and pulmonary valve insufficiency was found in 50.0% of the induction group and in 8.7% of the control group (p=0.026). There were no significant differences between groups concerning aortic valve insufficiency, left ventricular ejection fraction, atrial diameters and septal thickness. Finally, there was also a significant difference between the median $CHAD_2S_2$-VASc scores, with the median score of 2 in the induction group and a score of 1 in the control group (p=0.04). A detailed summary can be found in [Table 1].

Development of Atrial Fibrillation During the Course of Follow-up

Surprisingly, only 5 out of 62 patients were diagnosed with newly onset atrial fibrillation during the total course of follow-up (2 patients with EPS-induced sustained AF, 1 patient with EPS-induced non-sustained AF, 2 patients without previously inducible AF). No single patient experienced symptoms pointing to stroke or TIA. After 3 months, 89.5% (17/19) of the patients with positive AF inducibility were free of atrial fibrillation in contrast to 100% (43/43) of those with a negative inducibility status (p=0.031). At 3 years, the Kaplan-Meier analysis estimated an event-free survival rate of 84.2% in the induction group and 88.9% in the control group, clearly missing statistical significance (p=0.162, [Figure 2]).

Discussion

Our results show that AF inducibility in patients without a history of AF is more likely in an older population as well as in those patients who have a lower glomerular filtration rate, who suffer of mitral, tricuspid an pulmonary valve insufficiencies of any degree and finally in patients who have a $CHAD_2S_2$-VASc score of 2 or more. Furthermore, the study suggests that patients with a positive AF inducibility status are more often diagnosed with symptomatic atrial fibrillation within the first months after EPS, while those with

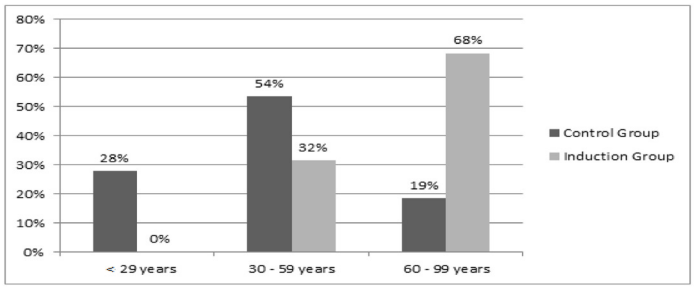

Figure 2: Age distribution stratified by inducibility status and age intervals.

a negative inducibility seemed to remain free of new-onset atrial fibrillation for up to 2.5 years after testing. The loss of a statistically significant difference between both groups in the long term could possibly be explained by a temporarily limited value of the results generated by electrophysiological testing, since all patients who were affected in the induction group developed atrial fibrillation within a very short time after being tested (up to 5 months), while the individuals of the control group who developed AF showed the first episodes more than 2.5 years after their EPS. We hypothesize that this could be explained by a gradual development of pathways capable of supporting AF in those patients who were initially non-inducible, possibly due to the lack of such pathways or fibrotic tissue, but were affected by remodelling processes in the meantime. Interestingly, in patients with positive inducibility, the duration of EPS-induced atrial fibrillation (non-sustained AF vs. sustained AF) respectively the time to conversion back to sinus rhythm was not necessarily associated with outcome. Studies with more participants are needed to evaluate whether there are other distinctive clinical features that are shared by those patients with a positive inducibility status and a subsequent development of symptomatic atrial fibrillation but are non-existent in those with a previous positive inducibility and ongoing freedom from the disease.

This study is also the first to our knowledge investigating the prognostic value of AF inducibility in a representative sample of cardiovascular patients, including also the chronically ill and those with structural heart disease, yet featuring only patients without pre-diagnosed atrial fibrillation and atrial flutter at the time of undergoing EPS, as previous studies were conducted to evaluate either whether the inducibility status following pulmonary vein isolation or isthmus ablation was predictive of the outcome (meaning that most patients were already diagnosed with atrial fibrillation in the first place) or included only overall healthy patients without structural heart disease. Essebag et al were amongst that first group and demonstrated in that context, that 82% of all patients with a negative inducibility via atrial burst stimulation (with or without the administration of isoproterenol) immediately after pulmonary vein isolation were free of atrial fibrillation 6 months later, in contrast to only 59% of patients with a positive inducibility status (72% vs 53% after 12 months)[13]. Haïssaguerre et al compared the efficiency of pulmonary vein isolation and linear ablation and additionally if noninducibility afterwards was a predictive factor. After 7±3 months, reoccurrence of arrhythmia was detected in 38% of the inducible and in 13% of the noninducible patients, showing statistical significance[14]. Oral et al also performed left atrial radiofrequency circumferential PV ablation with additional ablation lines in the posterior left atrium and the mitral isthmus and tested the inducibility status afterwards, with patients with a positive inducibility despite the preceding procedure undergoing either further catheter ablation (left anterior septum/ roof/ anterior wall, guided by fractionated electrograms) or no therapy. Of those patients who were noninducible after the initial procedure or underwent further ablation because of a positive inducibility, 85% were free of atrial fibrillation at the point of 6 months, compared to 67% of those who still had spontaneous or inducible episodes of atrial fibrillation[15].

In contrast, Kumar et al were amongst the second group and investigated the inducibility of atrial fibrillation in 44 mainly healthy patients without pre-known AF, yet also without structural heart disease. Induction was performed via high rate atrial pacing/ decremental pacing, with 10 successive repetitions in each patient, provoking atrial fibrillation of at least 1 minute duration in 49.5% of all patients and of more than 5 minutes in 29.5%, with the risk increasing with each repetition. In their study, neither was EPS-induced atrial fibrillation (sustained more than 5 minutes) linked to any clinical feature (besides male gender), nor did a single patient develop clinical episodes of atrial fibrillation or any other tachycardia affecting the atrium during a median follow-up time of 23 months, though the exact modalities of follow-up were not explicitly listed[16]. Joza et al published a study regarding the prognostic value of AF induction in patients who underwent right atrial flutter ablation before. Around the onset of follow-up, a subgroup of 93 patients was without a history of atrial fibrillation (yet still with a history of atrial flutter). Burst stimulation was performed over 5 seconds at first from the anterolateral right atrium and subsequently from the coronary sinus, with positive inducibility defined as sustained atrial fibrillation over the course of 30 seconds. 20 patients were counted as inducible, 73 as not inducible. During the course of follow-up, 14 out of 20 patients with positive inducibility developed atrial fibrillation in contrast to 5 out of 73 with negative inducibility (crude Hazard Ratio = 13.74)[17]. Finally, Leong-Sit et al investigated the prognostic value of the induction of atrial fibrillation and atrial flutter after pulmonary vein isolation as well, but focused also on factors associated with positive inducibility. During their follow-up, 49.1% of the patients with negative inducibility and 49.4% of those with positive inducibility had a relapse, contradicting the quintessence of the majority of other studies conducted regarding this topic and clearly missing statistical significance. Positive inducibility was in consistence with our results significantly associated with age (per decade, OR 2.10). A history of hypertension (OR 4.15) was also identified as a positive predictor, whereas diabetes mellitus was a negative predictor of inducibility (OR 0.06), probably being caused by a type I error according to the authors[18].

Study Limitations

Since our study was conducted retrospectively, it is subject to the characteristic corresponding disadvantages. With only about half of the members of both groups receiving Holter ECGs or interrogations

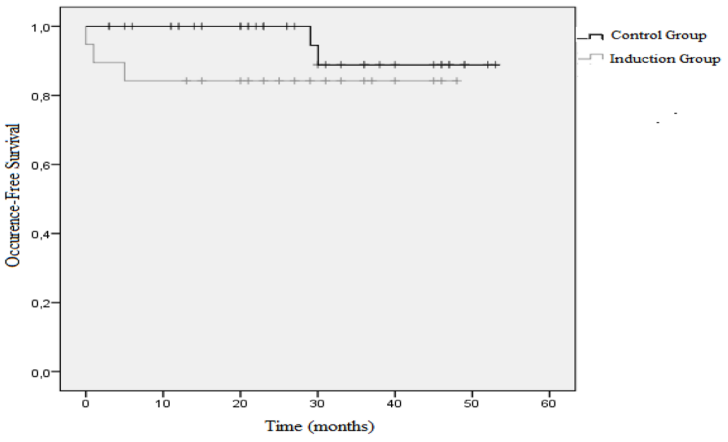

Figure 3: Kaplan-Meyer estimation, illustrating the event-free survival during the maximum course of follow-up, stratified by inducibility status.

of ICDs/ pacemakers/ event recorders and most of the remaining patients only routine 12 channel ECGs, patients could have been left undiagnosed, as the study design enabled only the reliable detection of persistent or symptomatic atrial fibrillation in contrast to the currently intensely debated asymptomatic paroxysmal atrial fibrillation, though on the other hand the significance of asymptomatic atrial fibrillation is still not ultimately ascertained[19]. In addition, since a positive inducibility status was associated with a higher age and certain comorbidities, it is possibile that AF inducibility during EPS is not an independent predictor, but merely a marker for older patients or such with a degrading health status, who then again are known to be at higher risk for developing atrial fibrillation subsequently. Further analysis addressing that issue was not feasible due to the small number of patients included. Due to this underpowering, a final statement regarding the prospective value of EPS-induced AF cannot be made at this point. Another perhaps more fundamental problem in comparing various studies investigating the prognostic value of induced atrial fibrillation is the lack of a broadly accepted (and adhered to) standard protocol regarding the invasive procedure. Some of the differences between various studies could thereby be possibly explained by different pacing protocols (e.g. time, minimum CL, repetitions, use of catecholamines) and different definitions of the term inducible (especially the required time for being classified as such, varying from multiple minutes to only a few seconds).

Conclusion

Inducibility of atrial fibrillation via burst pacing during EPS in patients without a documented history of AF and atrial flutter seems to be associated with a subsequent higher risk of clinical atrial fibrillation. The prognostic value seems short-termed, since 2.5 years after testing the first members of the control group were also diagnosed with AF. Three years after testing, no statistically significant difference was left between both groups. Patients with a positive inducibility status were found to have a significantly higher age, a lower GFR, a higher rate of various valve insufficiencies and, more generally, a higher $CHAD_2S_2$-VASc score than their counterparts. As the numbers are too small and the current state of knowledge is not sufficient for discussing possible further consequences for patients with a positive inducibility status (e.g. prophylactic anticoagulation), we emphasize the so far more impressive and potentially clinically useful negative predictive value of the test, since all of our patients with a negative inducibility were free of diagnosed atrial fibrillation up to 2.5 years after testing. As our study was designed as an exploratory study, subsequent studies could also be performed in a prospective setting, employing patients with a planned implantation of a DDD-pacemaker, as most pacemakers would enable standardised atrial burst pacing (ideally during the implantation process) as well as a continuous follow up.

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Atrioventricular Nodal Catheter Ablation in Atrial Fibrillation Complicating Congestive Heart Failure

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Abstract

The development of atrial fibrillation (AF) during the course of the evolution of heart failure (HF) worsens the clinical outcomes and the prognosis accounting for an enormous economic burden on healthcare. AF is considered to be an independent predictor of morbidity and mortality increasing the risk of death and hospitalization in 76% in HF patients. Despite the good clinical results obtained with conventional pharmacological agents and different new drugs, the optimal medical treatment can fail in the intention to improve symptoms and quality of life of HF patients with severe left ventricular dysfunction and AF with uncontrolled ventricular rate. Therefore, the necessity to utilize cardiac devices to perform cardiac resynchronization therapy (CRT), or the need to use catheter ablation, or both, emerges facing the failure of optimal medical treatment in order to achieve hemodynamic improvement. Some of these AF patients will require atrio-ventricular nodal (AVN) catheter ablation in order to restore 100% CRT functionality and improvements in clinical outcomes. It is hard to imagine that the deliberate destruction of a natural and normally functional specialized tissue of the main conduction system of the heart would do any good. However, in the presence of AF with rapid ventricular response due to normal conduction through the AV node in HF patients, the fast ventricular rate can cause deleterious consequences in the clinical outcome. Moreover, there are interesting published data which will be analyzed in this manuscript documenting significant acute and long-term improvement in left ventricular function, symptoms, exercise tolerance, clinical outcomes, and quality of life in selected HF patients with paroxysmal and persistent drug-refractory AF who have undergone AVN ablation and permanent pacemaker implantation.

Introduction

Atrial fibrillation (AF) and heart failure (HF) are common cardiovascular entities with high comorbidities and mortality and severe prognostic implications. The development of AF during the course of the evolution of HF worsens the clinical outcomes and the prognosis accounting for an enormous economic burden on healthcare[1-5]. Once AF develops, it generates rapid ventricular response, irregularity of ventricular rhythm, loss of organized atrial contribution to cardiac output, and in some cases, tachycardia-induced cardiomyopathy[6-13]. It has been shown that aging has a profound impact on the histological and thus, electrophysiological changes in the human atrial myocardium which contribute to the higher prevalence of AF in the elderly[14-20]. The prevalence of AF in patients with advanced HF reaches up to 40%. AF is considered to be an independent predictor of morbidity and mortality increasing the risk of death and hospitalization in 76% in HF patients[11-13].

Despite the good clinical results obtained with conventional pharmacological agents and different new drugs, the optimal medical treatment can fail in the intention to improve symptoms and quality of life of HF patients with severe left ventricular dysfunction and AF with uncontrolled ventricular rate[21-24]. Therefore, the necessity to utilize cardiac devices to perform biventricular pacing, or the need to use catheter ablation, or both, emerges facing the failure of optimal medical treatment in order to achieve hemodynamic improvement and correction of the physio-pathological alterations. Several clinical studies with cardiac devices performing biventricular pacing demonstrated structural and functional ventricular improvement. In addition, there are beneficial effects of this so called cardiac resynchronization therapy (CRT) in left ventricular remodeling. There was a significant improvement in left ventricular ejection fraction, and a significant decrease in end systolic and end diastolic volumes at 3 months of follow-up[25,26]. Importantly, these beneficial effects are dependent on continuous bi-ventricular stimulation since interruption of electric stimulation produce a progressive but not immediate loss of effect. However, CRT may be interrupted in over one-third of patients after successful implantation of a device and the most common reason for CRT interruption is the development of AF (18%). Indeed, almost one fifth of patients who undergo successful implantation of a defibrillator capable of delivering CRT experience an AF with a rapid ventricular response, which at least temporarily results in the inability to deliver CRT[25-27]. Some of these patients will require atrioventricular nodal (AVN) catheter ablation in order to restore 100% CRT functionality and improvements in clinical outcomes. Therefore, it is the aim of this manuscript to analyze the interesting published data documenting significant acute and long-

Key Words

AVN Ablation, Atrial Fibrillation, Heart Failure, Pacemaker Implantation.

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term improvement in left ventricular function, cardiac performance, symptoms, exercise tolerance, clinical outcomes, and quality of life in selected HF patients with paroxysmal and persistent drug-refractory AF who have undergone AVN ablation and permanent pacemaker implantation.

Atrioventricular Nodal Catheter Ablation

In 1982, way before the existence of current techniques for catheter ablation of atrial fibrillation, Gallagher JJ et al described the percutaneous catheter technique for the ablation of the atrioventricular conduction system[28]. It is hard to imagine that the deliberate destruction of a natural and normally functional specialized tissue of the main conduction system of the heart would do any good. However, in the presence of AF with rapid ventricular response due to normal conduction through the AV node, the fast ventricular rate can cause deleterious consequences in the clinical scenario. There is a further frank deterioration in the outcome if the left ventricle is dysfunctional. Therefore, catheter ablation of the AV node was utilized to create complete AV conduction block in order to control the ventricular rate in AF patients[28]. In order to preserve a junctional escape rhythm, catheter ablation of the proximal AV junction is performed. Hence, ablation is usually targeted at the atrial side of the annulus in the region of the compact AV node in the vicinity to the anterior border of the coronary sinus ostium [Figure 1]. Ablation of the AV node does not restore physiologic atrial systole and associated atrial transport. Therefore, the beneficial effects of catheter AVN ablation are mediated primarily by restoration of physiologic rate and possibly by regularization of the ventricular response to concomitant AF[29-33]. Although those symptoms that result from a fast and irregular ventricular rate may show dramatic improvement, the symptoms that occur from the loss of atrial contraction and AV synchrony are unlikely to improve. This procedure leads to rate control but not rhythm control, hence, the atria will keep on fibrillating, and the ventricular response will dependent on the implanted permanent pacemaker [34-39].

Clinical Outcomes in AVN Ablation Studies

In general, several retrospective studies, randomized control studies, and meta-analysis reported beneficial evidence that AVN catheter ablation followed by permanent pacemaker implantation are a valuable palliative therapy for highly symptomatic, drug-refractory AF patients. Many retrospective studies have documented significant acute and long-term improvement in left ventricular function, symptoms, cardiac performance, exercise tolerance, clinical outcomes, and quality of life in selected patients with paroxysmal and persistent drug-refractory AF who have undergone AVN ablation and permanent pacemaker implantation[30-37].

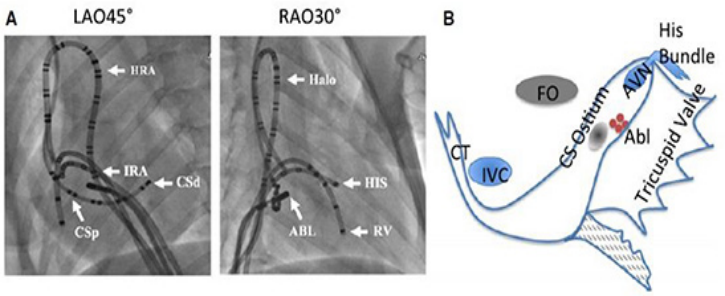

Figure 1: This figure depicts radiofrequency AVN ablation at the bottom of Koch's triangle. A: Catheter position. B: Koch's triangle and ablation sites.

ABL: indicates radiofrequency ablation sites. CSd: distal coronary sinus. CSp: proximal coronary sinus. CT: crista terminalis. FO: fossa ovalis. Halo: Halo catheter. HIS: His bundles. HRA: high right atrium. IRA: inferior right atrium. IVC: inferior vena cava. LAO: left anterior oblique. RAO: right anterior oblique. RV: right ventricle. Reprinted with permission from Yin X, et al. Atrioventricular Node Slow-Pathway Ablation Reduces Atrial Fibrillation Inducibility: A Neuronal Mechanism. J Am Heart Assoc. 2016;5:e003083 doi:10.1161/JAHA.115.003083.

There have also been several randomized controlled trials comparing AVN ablation followed by pacemaker insertion strategy with medical therapy[40-43]. Brignole M et al observed that ablation and placement of a DDDR mode-switching pacemaker were highly effective and superior to drug therapy in controlling symptoms and improving quality of life in patients with intolerable paroxysmal AF not controlled with antiarrhythmic drugs[43]. The same authors found similar finding in patients with chronic AF who had clinically manifest HF and underwent VVIR pacemaker implantation after AVN ablation[42]. Like these two mentioned studies by Brignole et al, which all together had only 109 patients, many of the randomized studies had small number of patient and could have been affected by patient selection bias. On the other hand, those clinical studies examining patients with paroxysmal AF may not have demonstrated improvements in exercise tolerance because of the intermittent nature of the tachyarrhythmia. Additionally, hemodynamic improvements may be subjected to the etiology of the left ventricular dysfunction and may only happen in patients with tachycardia cardiomyopathy, which is known to be mostly a reversible entity[37,39,42,44].

Some meta-analysis reported also beneficial evidence in favor of AVN catheter ablation followed by permanent pacemaker implantation in symptomatic, drug-refractory AF patients. Wood MA et al.[45] examined 1181 patients from 21 different studies and found that exercise duration, ejection fraction, quality of life, symptoms, and hospital admissions improved significantly. In their meta-analysis they observed that the only parameter that did not reach statistical significance was LV fractional shortening. However, this last parameter showed a tendency towards improvement. Chatterjee NA et al.[46] analyzed a total of 5 randomized or prospective trials with a total of 314 patients for efficacy review, another 11 studies (810 patients) for effectiveness review, and 47 studies (5632 patients) for safety review. These authors found in their meta-analysis that in the therapeutic management of refractory AF, AVN catheter ablation is associated with improvement in symptoms and quality of life, with a low incidence of procedure morbidity[46]. In addition, in patients with reduced systolic function, AVN ablation demonstrated also significantly improved echocardiographic outcomes relative to medical therapy alone. However, their results demonstrated also that there was no statistical difference in all-cause mortality, exercise duration, and left ventricular ejection fraction between AVN ablation and medical therapy groups[46].

Permanent Pacing After AVN Catheter Ablation

In order to avoid the deleterious effects of long-term right ventricular pacing on left ventricular function after AVN catheter ablation[47], biventricular pacing, to implement cardiac resynchronization therapy, has been proposed as an alternative to right ventricular pacing. CRT significantly reduces hospitalizations for HF, and significantly improves functional capacity, and left ventricular function, volumes and diameter in comparison with

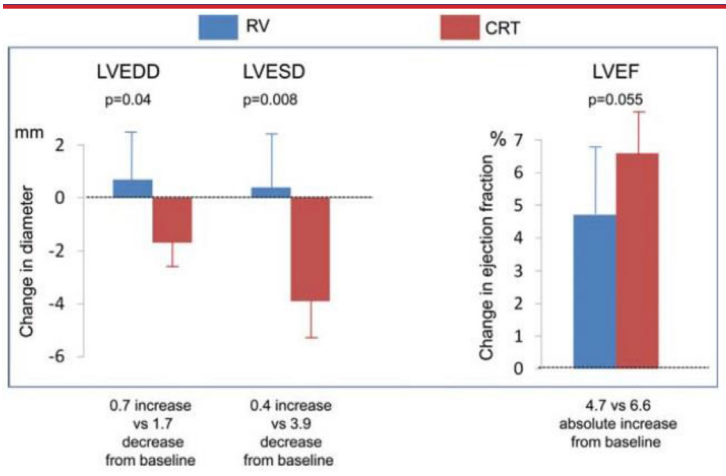

Figure 2: **Mean changes in echocardiographic left ventricular diastolic and systolic diameters and ejection fraction between baseline and 6-month follow-up.**

RV: right ventricular pacing. CRT: cardiac resynchronization therapy. LVEDD: Left ventricular end diastolic diameter. LVESD: Left ventricular end systolic diameter. LVEF: Left ventricular ejection fraction. Reprinted with permission from Brignole M, et al. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. Eur Heart J 2011;32:2420-2429.

right ventricular pacing only [Figure 2][48-50]. Therefore, the current guidelines recommend CRT in patients with AF and left ventricular dysfunction who are candidates for AVN catheter ablation with an indication IIa level of evidence B[51,52]. Indeed, AVN ablation followed by CRT is an established strategy for improving symptoms and morbidity in patients with permanent AF, reduced left ventricular ejection fraction, and uncontrolled ventricular rate.

Patients with AVN ablation become totally pacemaker dependent with iatrogenic chronotropic incompetence. They lose the ability to increase their heart rate appropriately during physical activity. However, this condition may be corrected by the use of rate-adaptive pacing. In this context, Palmisano P et al[53] performed a prospective, randomized, single-blind, multicenter study that was designed as an intra-patient comparison and enrolled 60 patients with refractory AF and reduced left ventricular ejection fraction treated with AVN ablation and biventricular pacing. They compared the clinical effects on exercise capacity of rate-responsive pacing versus fixed-rate pacing in CRT. They found that rate-responsive pacing yields a significant gain in exercise capacity, which seems to be related to the induced increased heart rate during physical exercise [Figure 3A&B]. However, these good results with CRT were not observed with right ventricular pacing alone in another smaller study in patients with preserved left ventricular systolic function[54]. We have to keep in mind that while rate-responsive pacing can help these patients to adapt their cardiac output to increasing metabolic requirements during exercise, it can also elicit an inappropriate and excessive increment in heart rate with possible deleterious effects[55]. This is especially true in pacemakers based on motion sensors in patients with AF and left ventricular dysfunction. An excessive increase in heart rate could further worsen the left ventricular diastolic function, which is already compromised by reduced compliance, and the absence of the atrial systole[56-59].

Collateral Adverse Effects of the Ablate and Pace Approach

Probably the main concern with this "ablate and pace" approach is sudden cardiac death. Twenty years ago Geelen P, et al[60] roused some concern about AVN catheter ablation and permanent pacemaker implantation. They stated that this approach may predispose patients to an increased risk of sudden cardiac death[60]. Early studies are conflicting however, with 1 year sudden death rates varying from 0 to 9%[45,61]. It is important to note that the vast majority of those who experienced sudden cardiac death in the early studies had a significant number of risk factors, including reduced left ventricular function, advanced HF, and a history of ventricular arrhythmias[62,63]. Since the probable mechanism of sudden cardiac death is bradycardia-dependent prolongation of the QT interval, this may be counteracted by incrementing the pacemaker frequency[60,64]. It was recommended to set the pacemaker at a ventricular pacing rate of minimum of 90 bpm for the first 1 to 2 months following the ablation, and then reducing it to a conventional 60 to 70 bpm [60,65]. This latter approach was corroborated by large studies with long-term follow-up which demonstrated a low incidence of sudden cardiac death[66,67]. Bradley DJ et al.[68] demonstrated an all-cause mortality of 3.5% with AVN ablation and 3.3% with drug therapy at 1 year of follow-up in their

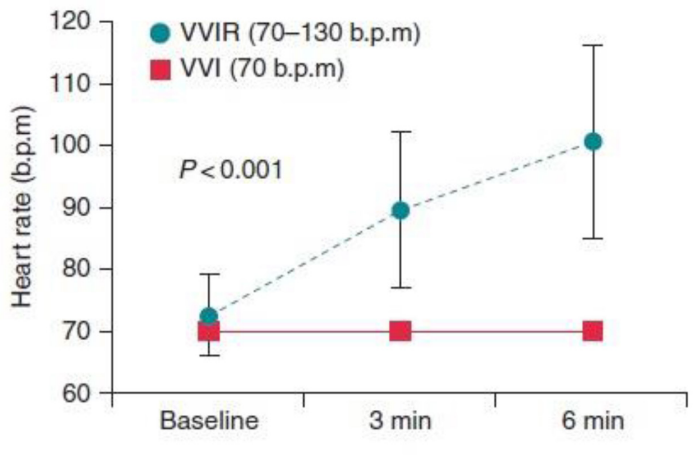

Figure 3A: **A-Mean heart rate during six-minute walking test in VVI pacing mode (solid line) and in VVIR pacing mode (dotted line).**

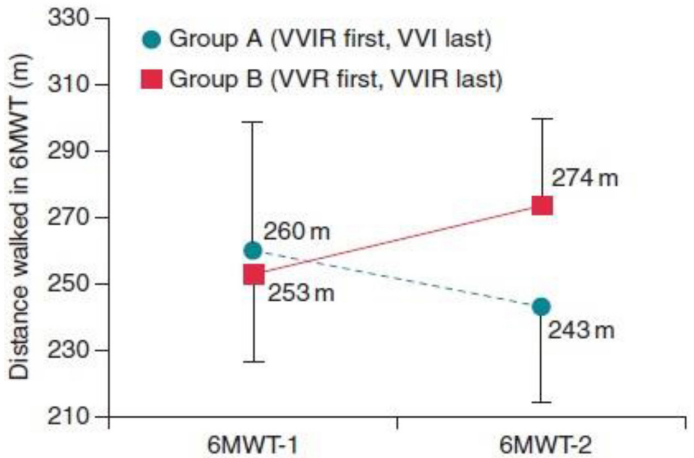

Figure 3B: **B-Mean distance walked during six-minute walking test-1 and 2 by Group A and Group B patients.**

Group A began exercising with VVIR pacing mode first, and then VVI pacing mode last. Group B began exercising with VVI pacing mode first, and then VVIR pacing mode last. Reprinted with permission from Palmisano P, et al. Effect of fixed-rate vs. rate-RESPONSIve pacing on exercise capacity in patients with permanent, refractory atrial fibrillation and left ventricular dysfunction treated with atrioventricular junction aBLation and bivEntricular pacing (RESPONSIBLE): a prospective, multicentre, randomized, single-blind study. Europace 2017;19:414-420.

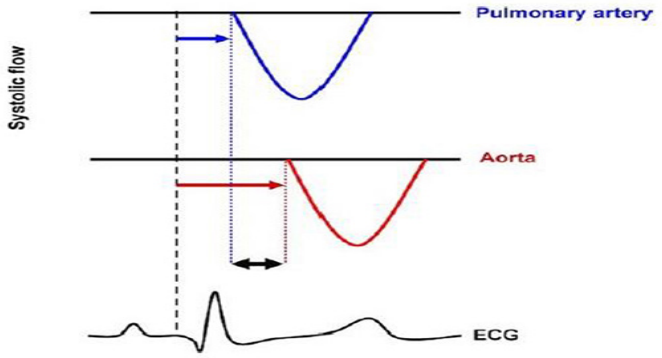

Figure 4A: Schematic representation of interventricular dyssynchrony during RV apical pacing for assessment of interventricular dyssynchrony. The electrocardiogram (ECG) and systolic flow through the pulmonary artery and aorta assessed with Doppler echocardiography are typically used. Both the right ventricular (RV) and left ventricular (LV) electromechanical delay are measured from the onset of the QRS complex (dashed line). The RV electromechanical delay is the time from the onset of QRS interval to the onset of pulmonary systolic flow (blue arrow). The LV electromechanical delay is the time from the onset of QRS complex to the onset of aortic systolic flow (red arrow). Subsequently, the interventricular dyssynchrony can be calculated as the difference between the RV and the LV electromechanical delays (black arrow).

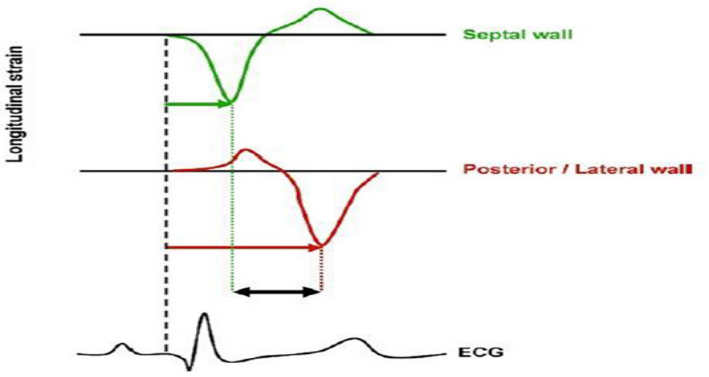

Figure 4B: Schematic representation of intraventricular dyssynchrony during RV apical pacing. Intraventricular dyssynchrony is represented by the delay in mechanical activation between different segments within the LV. In this example, longitudinal strain curves of the septum and the posterior or lateral wall are demonstrated. The time from onset of the QRS complex to peak systolic strain for the septum (green arrow) and the posterior or lateral wall (red arrow) is indicated. The difference in time-to-peak strain for the various segments is the delay in mechanical activation, or LV intraventricular dyssynchrony (indicated by the black arrow). Reprinted with permission from Tops LF, et al. The effects of right ventricular apical pacing on ventricular function and dyssynchrony: implications for therapy. J Am Coll Cardiol 2009;54:754-776.

meta-analysis of randomized trials comparing AVN catheter ablation with permanent pacemaker implantation and drug therapy. In a recent meta-analysis, Chatterjee et al.[46] reported that the incidence of procedure-related mortality within 30 days of AVN ablation was 0.27% among 4886 patients from 42 studies. At a mean follow-up of 26.5 months, the incidence of sudden cardiac death after AVN catheter ablation was 2.1%.

The heart rate post-AVN catheter ablation plays an important role in sudden cardiac death[46]. Ozcan C et al.[63] observed an overall rate of sudden death after AVN ablation and permanent pacemaker implantation of 2.1% when pacing at a lower rate limit of 60 bpm. On the other hand, Wang RX et al.[69] found that the rate of sudden death decreased to 0.2% when pacing at an initial lower rate of 90 bpm. These results suggested that AVN catheter ablation predisposed patients to bradycardia dependent pro-arrhythmia. Therefore, it is necessary to utilize this pacing rate algorithm in order to improved clinical outcomes and survival[69].

There are uncertainties about the exact mechanism underlying sudden cardiac death after AVN catheter ablation. It has been reported that long-term right ventricular pacing can induce electrical and mechanical LV inter-ventricular and intra-ventricular dyssynchrony in almost 50% of patients[70-73] [Figure 4]. Yan et al.[73] reported that ventricular dyssynchrony is associated with pro-arrhythmic repolarization dispersion. Chronic dyssynchrony leads to chamber remodeling of both early- and late-activated segments[74]. Experimental studies have shown that LV pacing via the coronary sinus promotes arrhythmogenesis due to a pacing-induced increase in QTc and QT dispersion with increased transmural dispersion of repolarization involving the mid-myocardial M cells[75]. Medina-Ravel VA et al.[76] suggested that CRT may enhance arrhythmogenicity by reversing the normal depolarization pattern from endocardium to epicardium, which enhances transmural dispersion of repolarization and propagation of early afterdepolarizations[76]. In addition, pacing-induced changes in QTc and QT dispersion may be related to the risk of sudden cardiac death in patients undergoing CRT[77,78]. Nowadays, sudden cardiac death is not a subject of concern in the "ablate and pace" approach[79,80] [Figure 5]. The 1 year total mortality is 6.3% and the rate of sudden cardiac death is only 2%, which is similar to that of control patients with atrial fibrillation who remain on drug therapy [45,66].

Another concern with this "ablate and pace" approach is the subsequent alteration of the left ventricular function due to permanent right ventricular apical pacing. Some studies asserted conceived concern about rendering a patient dependent upon right ventricular apical pacing following AVN catheter ablation stating that it may lead to further deterioration in left ventricular function[44,81-83]. Right ventricular apical pacing can cause harmful effects due to ventricular dyssynchrony, remodeling, and prolonged QRS durations[81]. It has been observed that constant right ventricular apical pacing may lead to increased mortality, and hospital admissions due to HF, especially in patients who already have significantly impaired left ventricular function[82]. However, there is an interesting controversy on this subject in the published studies. Indeed, the effect on left ventricular function and clinical outcomes of HF are not consistent in the literature, with some studies showing some degree of deterioration [44,83] with others showing no significant change[37,42], and several other studies demonstrating an overall improvement[34,37,39,45]. This important discrepancy may be related to the high proportion of patients with normal left ventricular function included in the majority of studies. In addition, it may also be associated to the initial mechanism of left ventricular dysfunction and HF symptoms. For example, patients with tachycardia cardiomyopathy, show reversible changes when appropriate rate control is achieved. Ozcan C et al.[66] showed that long-term survival after AVN catheter ablation was comparable with that in AF patients with pharmacological therapy. Moreover, when adjusted for underlying heart disease, survival

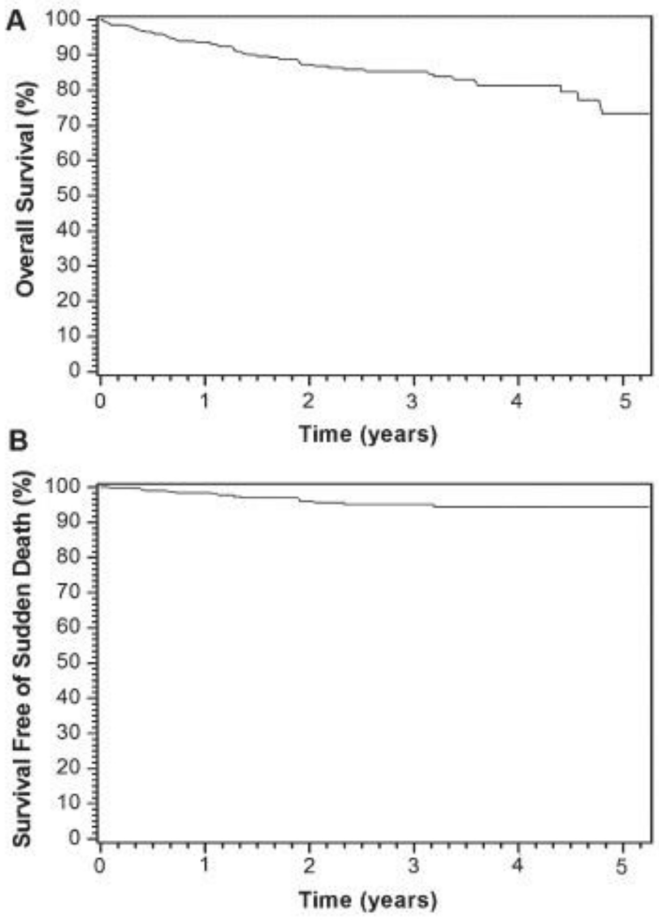

Figure 5: Kaplan-Meier estimated (A) overall survival and (B) survival free of sudden death in patients who underwent atrioventricular junction ablation and device implantation. Reprinted with permission from Wang RX, et al. Sudden death and its risk factors after atrioventricular junction ablation and pacemaker implantation in patients with atrial fibrillation. Clin Cardiol 2017;40(1):18-25.

was similar to the expected survival in the general population. Bjorkenheim A. et al.[83] showed that long-term right ventricular pacing was not harmful in the majority of AF patients after AVN catheter ablation. They identified hypertension and previous HF as independent predictors of all-cause mortality, and prolonged QRS duration and left atrial diameter as predictors of hospitalization for HF during long-term follow-up[83]. They also found that all-cause mortality occurred in 22%, which is similar to the 26% in the study of Tan ES et al[84]. This latter study had a slightly shorter follow-up period[84]. The PAVE study[49]randomized 184 patients with a mean left ventricular ejection fraction of 46% to biventricular pacing or right ventricular pacing. In 83% of the patients, class II or III heart failure was present. Both groups showed an improvement in 6 min walk distance compared with baseline. Of interest is that the two pacing modalities did not differ until 6 months after the procedure, when a small deterioration in the right ventricular pacing group resulted in a significant difference between the two groups. The right ventricular pacing group showed a significant fall in left ventricular ejection fraction within 6 weeks which persisted at 6 months[49]. On the other hand, the ejection fraction in the biventricular pacing group did not change from baseline values. Patients with impaired left ventricular function at baseline who underwent biventricular pacing showed the greatest improvement. Furthermore, patients with class II or III heart failure who received biventricular pacing improved significantly more than those who received right ventricular pacing. There was a 14% failure of left ventricular lead implantation[49].

Alternative Pacing Modalities

Besides CRT, several pacing techniques have been used to subside the potential alterations of right ventricular apical pacing, including right septal, right ventricular outflow tract, para-Hisian, and direct His bundle pacing. Direct His bundle pacing produces an activation sequence closest to normal physiological activation, and in dilated cardiomyopathy, patients can avoid further deterioration in left ventricular ejection fraction[85-87]. Occhetta E, et al.[88] in a crossover, blinded, randomized study demonstrated good results in the prevention of ventricular desynchronization by permanent para-Hisian pacing after AVN catheter ablation in chronic AF patients. They found that in those HF patients with cardiac co-morbidities and reasonably better left ventricular function, para-Hisian pacing produces improvements in functional status and exercise capacity when comparing to those patients with right ventricular apical pacing[88]. Huang W, et al.[89] demonstrated that permanent His bundle pacing is safe and stable in HF patients with AF who had narrow QRS and underwent AVN catheter ablation. They observed a significant improvement in functional class, and echocardiographic left ventricular ejection fraction, and reduction in the utilization of diuretics in the HF therapeutic management. The success of the His bundle pacing depends upon several factors. The distal portion of the His-Purkinje system to the pacing site should be normal. In addition, the AVN catheter ablation should be performed at the atrial site of the AV node rather than at the site of the His bundle. Considering that patients are rendered pacing dependent permanently, there are also concerns about the stability of an active fixation lead at a site so close to the tricuspid valve. The results of septal and outflow tract pacing are inconclusive [90,91]. Twidale N, et al. in a comparative trial in patients with congestive HF and uncontrolled AF demonstrated that complete AV node ablation and pacemaker permanent implantation delivers a more substantial improvement in exercise capacity, quality of life, and left ventricular ejection fraction than AVN modification [61].

Conclusions

There is significant acute and long-term improvement in left ventricular function, cardiac performance, symptoms, exercise tolerance, clinical outcomes, and quality of life in selected HF patients with paroxysmal and persistent drug-refractory AF who have undergone AVN ablation and permanent pacemaker implantation. In this context, biventricular pacing is superior to right ventricular apical pacing, and even better with rate-responsive pacing modality which yields a significant gain in exercise capacity due to the induced increased heart rate during physical effort. Current guidelines recommend CRT in patients with AF and left ventricular dysfunction, whom are candidates for AVN catheter ablation with an indication IIa level of evidence B. Caution should be exerted since there is serious concern and controversial results with alternative pacing modalities.

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Coronary Sinus Electrograms May Predict New-onset Atrial Fibrillation After Typical Atrial Flutter Radiofrequency Ablation (CSE-AF)

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Abstract

Background: Complex fractionated electrograms (EGMs) of the coronary sinus electrograms (CSEs) are employed as a target during radiofrequency ablations (RFA) of atrial fibrillation (AF). Anatomically, CSEs includes both of left atrium (LA), coronary sinus musculature and right atrium (RA) electrograms.

Aim: To determine the significance of fractionated CSE and delayed potentials as a predictor of new-onset AF after radiofrequency ablation (RFA) of isolated atrial flutter (AFL).

Methods: Consecutive patients underwent AFL ablation. Fractionated and/or continuous discrete activities were recorded from coronary sinus electrograms during sinus rhythm and during pacing. Earliest CSE to the S nadir or peak R in milliseconds was recorded and considered as propagation delay for EGMs.

Results: Forty patients were included during a mean follow-up period of 55.1± 15.8 months. Twenty patients (50 %) developed AF while the remaining 20 patients maintained sinus rhythm(SR) during the follow-up period. Proximal and mid CSEs were significantly fractionated in AF group compared to group with no AF development (65 % and 60% Vs. 35 % and 30 %, p = 0.03, respectively). However, during pacing from distal duo-decapolar catheter (pole 1-2), distal CSEs alone were significantly fractionated (p < 0.05) compared to SR group. Significant delayed propagation of proximal CSE during pacing and in sinus rhythm were observed in AF group (12.3 ± 9.2 ms vs 7.1 ± 3.6 ms, p = 0.03) and (7.2 ± 2.9 ms Vs 8.1 ± 4.6 ms, p= 0.02) in the same order.

Conclusions: Incidence of AF is associated with fractionated proximal and mid CSE in sinus rhythm and distal CSE during paced rhythm after isolated AFL ablation. Delayed proximal CSE propagation is correlated with AF incidence.

Introduction

Cavo - tricuspid (CTI) radiofrequency ablation (RFA) is a standard treatment for common atrial flutter (AFL). Due to high safety profile and success rate, this procedure is appreciated as a first line of management[1]. Nevertheless, atrial fibrillation (AF) is commonly associated and documented after CTI ablations[2-5].

The coronary sinus is electrically connected to the right and left atrium and hence its signal obtained from this position reflect right and left atrial activities[6]. Fractionated atrial electrograms suggest inhomogeneous intra atrial conduction with great predisposition to develop AF[7]. Patients who develop AF post ablation have higher prevalence of proximal CS complex fractionation that, in turn, is associated with slowed electrical conduction[8].

The aim of our study was to assess whether the presence of fractionated CSE and delayed electrical conduction at coronary sinus os region are associated with a risk of developing AF after CTI ablation in patients undergoing typical flutter ablation and no prior history of AF. These parameters signify the role of Atrial scar burden in development of AF[6],[8],[9].

Key Words

Atrial Fibrillation, CSEs Represent Left Atrium, Radiofrequency Ablation (RFA), Cavo-tricuspid (CTI)

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Introduction

Methods

Patient Characteristics

The study was approved by Queen's University research and ethics board, Kingston, Canada. The retrospective cohort was selected from consecutive patients admitted to Kingston General Hospital for catheter ablation of common typical AFL from January 2008 to December 2011 were followed up over a time period of 55.1± 15.8 months. Most of the patients were at sinus rhythm (30/40, 75 %) with clearly documented typical AFL before admission to the cath lab.

Patients were excluded if they had: (i) redo-ablations, or history of any previous ablation (ii) non CTI-dependent circuits, (iii) use of antiarrhythmic drugs after the ablation, (iv) Patient underwent pacemaker implant and/or developed another atrial arrhythmias or (v) lost to follow-up records. Demographics, co-morbidities, history of cardiac disease, CHADS2 score and echocardiographic parameters

prior to ablation, including LA diameter and left ventricular ejection fraction (LVEF) were also collected during follow up. We have no patients with history of cardiomyopathy at the time of ablation.

Electrophysiology Study and Catheter Ablation

The coronary sinus was cannulated in all cases using a decapolar coronary sinus catheter (Abbott, St. Paul, MN, USA) with 2 mm interelectrode distance and 5 mm space between two electrode pairs. The proximal pair of electrodes was positioned at the coronary sinus ostium and the distal pair of electrodes was located at the lateral aspect of the great cardiac vein. Stability of the electrode catheters within the coronary sinus was maintained by fluoroscopic monitoring. A 20-poles (i.e. Halo) catheter (2-4-2 mm spacing) was positioned close to the anterior/superior tricuspid annulus (St. Jude Medical, St. Paul, MN, USA)

Ablation was performed using a 4-mm irrigated FlexAbility catheter (St. Jude Medical, St. Paul, MN, USA) positioned along the CTI until termination of atrial flutter and/ or the development of bidirectional block (in SR group). CTI block was accepted when (1) complete reversal of the right atrial depolarization on the 24-pole catheter when pacing in the coronary sinus, (2) conduction delays from proximal (i.e. CS 9-10 poles) to lateral CTI at distal Halo pole 1-2 (i.e. lower lateral right atrium) greater than any other intervals between those two points and the same apply other direction (i.e. lateral to medial)[10].

Study Protocol and Signal Recording

CS electrograms were analysed electronically off line using computerized recording system (Cardiolab System by Prucka Engineering Inc., Houston, Texas). Bipolar electrograms were filtered at a frequency of 30– 500 Hz.

The total duration of the CS electrogram was measured from initial activation to electrogram termination. Total signal durations of proximal (C 9-10), mid (C 5-6) and distal (C 1-2) coronary sinus electrograms were recorded. CS electrograms within these locations with more than two deflections were considered fractionated signals [Figure 1 & 2]. Initial CS potential duration was defined as the interval from initial deflection to the peak or nadir of the initial wave [Figure 3]. An initial delay of potential propagation was defined as a wave with duration exceeding 10 ms [11]. Continuous signal recordings were performed with atrial pacing of a 600-ms drive train from lateral CTI electrode (lower lateral poles "poles 1-2") and also during sinus rhythm. For each patient a random window of 5 consecutive EGMs was examined during SR and pacing and median figure was documented for further statistical analysis. The fractionated signals were reported if there were more than 2 deflections[12].

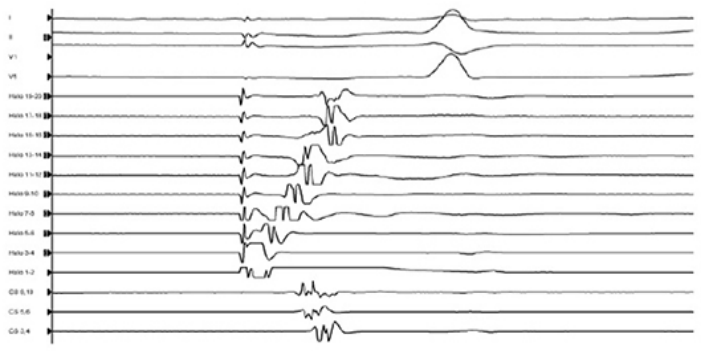

Figure 1: During lower right atrial pacing that demonstration fractioned distal CS Electrograms (Note C3-4 is the distal poles here)

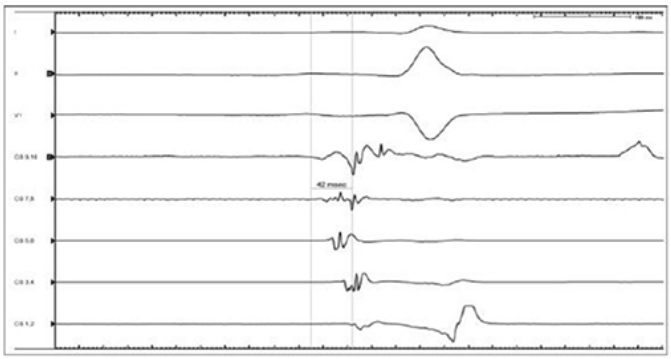

Figure 2: This figure demonstrate delayed potential >10ms and fractionated proximal CS electrogram during SR

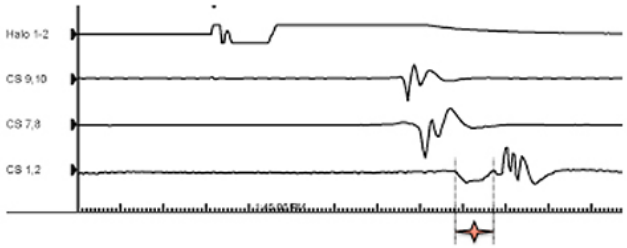

Figure 3: This figure illustrates another example of fractionated distal CS electrograms (CS 1,2) during lower right atrial pacing from Halo 1,2. Note also astrix interval to show an example of the measured delayed potential of CS component in distal CS.

Post-ablation Follow-up

We recorded a follow up period of 55.1± 15.8 months. Episodes of new-onset of AF occurrence with or without sustained fast atrial arrhythmia more than 30 seconds were identified from 12-lead ECGs, Holter monitoring and device interrogations. All patients (100% of patients) underwent a 12-lead ECG and 71% had a 24- or 48-hour Holter monitoring within 3 months of catheter ablation and then further follow up was arranged as routine (with ECG and Halters). Any documented symptoms of AF were also recognised.

Statistical Analysis

Data were analysed using SPSS software version 21.0 (SPSS, Chicago, IL, USA) and presented as mean ± standard deviation and median (interquartile range (IQR)). The distribution of the variables was analysed with the Kolmogorov–Smirnow test. Differences between two groups were tested using independent Student's t-tests for normally distributed variables, and the Mann Whitney U test was used for non-parametrically distributed variables. Differences between the categorical variables were analysed using the χ^2-test. A p-value of less than 0.05 was considered statistically significant.

Results

During the study period; a total of 40 patients fulfilled the inclusion

criteria and had complete follow up records. Baseline characteristics are summarized in [Table 1]. There were no significant differences between the two groups other than a lower LVEF in patients who eventually developed AF (61.4 ± 8.6 Vs.45.9 ± 22.4, p= 0.01) despite of matched atrial size (38.8 ± 6.9 Vs. 32.6 ± 17.6, P = 0.22) [Table 1]

Table 1: Baseline demographics and patients characteristics.

	SR	AF Occurrence	p-Value
Number of patients	20	20	N/A
38 (63.3)	19 (59.4)	19 (67.9)	0.50
Age (mean years ± SD)	65.2 ± 9.7	68.2 ± 8.7	0.30
Gender (Female, %)	7, 35 %	5, 25 %	0.24
LA size (mean cm ± SD)	38.8 ± 6.9	32.6 ± 17.6	0.22
LVEF (%)	61.4 ± 8.6	45.9 ± 22.4	0.01
History of CAD (n, %)	8, 40%	9, 45 %	0.32
History of OSA (n, %)	6, 30%	4, 20%	0.27
CHADS2 score (mean)	1	1.14	0.67
Hypertension (n, %)	(8, 40%)	(8, 40%)	0.76
Diabetes Mellitus (n, %)	(5, 25%)	(3, 15%)	0.44
Follow up (mean months ± SD)	54.3 ± 15.8	56 ± 16.1	0.73

LVEF = left ventricular ejection fraction, CAD = coronary artery disease and LA = left atrial size, OSA = obstructive sleep apnea.

Coronary Sinus Electrograms During Sinus Rhythm

During sinus rhythm, proximal coronary sinus electrograms(PCS) were significantly fractionated in AF group (30% vs. 65%; P = 0.03). The same observation was recorded in middle CS poles (30 % vs. 60 %, P=0.03). However, the initial conduction time of the electrograms, total electrogram duration and velocity from proximal to distal CS electrograms were comparable between both groups (p< 0.05)[Table 2].

Table 2: Coronary sinus electrograms during sinus rhythm.

	Control	AF occurrence	p-Value
CSp fractionation, n (%)	6 (30)	13 (65)	0.03
CSm fractionation, n (%)	6 (30)	12 (60)	0.03
CSd fractionation, n (%)	4 (20)	4 (20)	0.98
CSp electrical conduction time, ms	7.3 ± 3.5	11.5 ± 8.5	0.49
CSd electrical conduction time, ms	10.1 ± 3.8	10.7 ± 4.2	0.65
CSp total electrogram duration, ms	38.9 ± 11.6	45.5 ± 13.1	0.12
CSd total electrogram duration, ms	46.2 ± 11.9	43.0 ± 7.3	0.34
CSp to CSd duration, ms	75.0 ± 18.8	74.2 ± 11.3	0.87
Velocity, mm/ms	907.8 ± 438.6	972.3 ± 205.8	0.57

CSp = proximal coronary sinus, CSm = mid coronary sinus elecrogram, CSd = distal coronary sinus electrogram. All duration's measurements recorded in milliseconds (ms)

Description of Coronary Sinus electrograms during Atrial pacing

Pacing at cycle train of 600 ms from distal poles[1,2] from 20 poles duo-decapolar catheter has shown a significant delay in electrogram conduction at CS os (7.1 ± 3.6 Vs. 12.3 ± 9.2, P = 0.03), which was not associated with the same pattern in the distal CS electrograms (P = 0.52). Interestingly, distal CS electrograms were more fractionated in AF group when compared with control group (p < 0.05) during pacing.

Follow Up

Follow up period up to average of 56 month was recorded in both groups of patients. The period of follow up was comparable between AF group and controls (54.3 ± 15.8 months vs. 56 ± 16.1 months, p = 0.73).

Discussion

AF is commonly documented in isolated AFL and may occur in 50 % post AFL ablation[2]. This is extremely important as it impacts on the potential long-term outcome from AFL ablation and may influences the long-term oral anticoagulation management.

In this study, we carefully examined the standard coronary sinus electrograms - at the beginning of AFL ablation procedure - to predict AF occurrence. In our study, we examined the relationship between CS fractionation and CSEs potential delays in AF occurrences. This relationship highlight the role of high scar (i.e. as seen in fractionated CSEs) burden in AF development[6,8,9].

Table 3: Baseline demographics and patients characteristics.

	Control	AF occurrence	p-Value
Paced CSp fractination, n (%)	8 (40)	10 (50)	0.43
Paced CSm fractination, n (%)	6 (30)	11 (55)	0.15
Paced CSd fractination, n (%)	2 (10)	8 (40)	0.05
CSp conduction duration, ms	7.1 ± 3.6	12.3 ± 9.2	0.02
CSd conduction duration, ms	12.1 ± 7.0	10.8 ± 4.9	0.52
Paced CSp total EGMs duration, ms	41.2 ± 16.3	45.6 ± 19.6	0.47
Paced CSd total EGMs duration, ms	46.3 ± 9.7	44.4 ± 5.2	0.47
Paced CSp to CSd duration, ms	71.6 ± 19.9	71.3 ± 15.2	0.95
Paced velocity, mm/ms	1136.6 ± 417.3	1025.5 ± 238.7	0.31
CSE conduction duration >10 ms, n (%)	4 (20)	12 (60)	0.03

CSp = proximal coronary sinus, CSm = mid coronary sinus elecrogram, CSd = distal coronary sinus electrogram.

Major findings

In our study, half of the patients (50 %) developed AF during follow up period of 55.1± 15.8 months. This observation is previously well documented in isolated AFL underwent RF ablation treatment[4,13,14]. Chronologically, the highest occurrence rate of AF was documented in the first year of follow up (12/40 patients, 30 %). Then by the end of the second year we documented 16 patients that developed AF (40 %). In AF group, we found proximal and mid CS electrograms fractionated at SR and they developed easily greater potential delay during activation from lower lateral RA region. Moreover, distal CS (i.e reflecting LA fractionation) electrograms were remarkably fractionated with Rt lower atrial pacing.

Anatomical correlations of coronary sinus electrograms

Anatomic structure of the proximal CS is unique and quite complex. The CS os and proximal CS are surrounded by a cuff of a striated muscle which extends to the distal CS. The proximal CS OS is connected with the RA and similarly the mid to distal CS are well connected to the left atrium (LA)[15] as proven by the work of Antz et al[6,15]. In proximal CS electrograms, the right atrial components are depicted as initial sharp potentials and shorter duration while far field potentials of LA are at lower amplitude and longer duration. The opposite occurs in distal CS electrograms where LA EGMs are sharp[11]. More than 2 deflections in proximal and distal CS electro grams are considered pathological[12] and they may reflect scar volume.

Fractionated coronary sinus electrograms

Fractionated PCS electrograms represents RA source rather than LA only[16]. Yokoyama E et.al. found similar findings of fractionated EGMs and highest ratio of dominant frequency (DF) electrograms in proximal CS region in a non PV source of paroxysmal AF[17]. Moreover, another study documented higher prevalence of PCS fractionation and AF occurrence when seen in sinus rhythm CSE due to wave collusions at coronary sinus os due to slow propagation in presumably associated scar tissue[8,18]. This may support the importance of the results of our study of fractionated EGMs around PCS in SR within the group that developed AF. The mid CSE are also fractionated, and although the nature of CS musculature signals is quite complex, this still may emphasise the contribution of both the RA and CS future development of AF. Again, these findings were documented during SR. However, during lower right atrial pacing, distal CS electrograms became clearly fractionated, suggesting a possible intra left atrial inhomogeneous substrate (i.e. scar) for AF[7,19]. Various mechanisms may explain these findings. First, waveform frequencies increase, either by pacing or during AF fibrillation, will increase EGMs fractionation, duration and lead to re-entry in relation with the conduction disturbance. That mechanism of dynamics underlying conduction distortions was called percolation and was confirmed as a driver for AF initiation by Vigmond E et al[20]. Another theory is explained by tissue related anisotropy resulting in a ramble path of the propagating waveform. This occurs as a consequence to electrical uncoupling of the side-to-side connections between small groups of scars and fibrous tissue[21]. These explain the significance of complex fractionated CS electrograms in predicting AF[22]. This theory applied on distal CS signals which probably represents the scar burden in the LA.

Delayed atrial electrical potentials

Delayed electrical conduction is commonly seen in AF patients indicating intra-atrial conduction delay[9]. The existence of site-dependent intra-atrial conduction delays advocates non-uniform anisotropic characteristics of the posterior triangle of Koch may be critical for AF routers and induction. A possible explanation in the slow conduction in the post Kogh triangle may be required for reentry and may initiate AF[23]. In our study, we observed the same finding in the group who developed AF with delayed electrical propagation of proximal CS EGMs. This finding gives further insight into the potential pathophysiology underlying atrial fibrillation and the importance of the CS os region in AF development in our study.

Although the exact underlying pathophysiology undermining both AF & AFL is unclear, there are some electrophysiological properties similar to both[21]. Re-entrant mechanisms appear to be necessary for the development of AF along with abnormal intra-atrial conduction particularly in the posterior triangle of Koch[20]. As a result, it is not surprising that AF often develops in large proportion of patients post isolated AFL ablation that may result in a requirement for further RFA & reintroduction of medication. Predicting patients who may be at risk of developing AF post AFL ablation is not only provides useful insight into the pathophysiology underlying the development of AF but it may also influence treatment therapy post CTI including oral anticoagulation for high risk cohort for cerebrovascular events.

Study limitations

The limitations in the paper include the fact the sample size was quite small, retrospective study of 40 patients but it has a quite prolonged follow up period for 5 years. We believe this study may serve as a platform to continue investigating the low right atrium and its role in the development of AF post AFL ablation.

Moreover, while paced electrograms are expected to be more fractionated at the CS os and mid CS, the opposite was documented in our study. The explanation is that we kept pacing at slow rate at CL of 600 ms without added extrastimuli (i.e. which probably mimic most of the cathlab cases flow and protocols). Also, when Ching Tui et al. reported increased fractionation, that was in the context of increasing stimulus prematurity at faster CL than what we used in our paper. However, delayed potentials in CS os was clear in both paced and during intrinsic SR. Another limitation is the fractionated signals were documented in SR, and we had no AF patients to study the correlations of these signal during AF. However, these fractionations were not rate related as the velocity was comparable in both groups during SR and paced rhythm to suggest a scar related fractionations. Despite of a lower EF noted in AF occurrence group, the LA size over not different in both groups. On the other hand, previous studies demonstrated that patients with and without LVSD had similar risk for recurrent AF or AT after catheter ablation[24]. Moreover, none of the study cohort has underlying cardiomyopathy process in the history. We believe further investigation needs to be performed questioning whether the extent of fibrotic remodeling within the RA/ LA from a reduction in EF may contribute directly to these electrophysiological findings in this study.

Conclusion

Atrial fibrillation incidence is associated with fractionated proximal and mid CSE in sinus rhythm and distal CSE in paced rhythm. Delays of proximal CSE potentials during sinus and paced rhythm are correlated with AF occurrence. Further studies to validate these findings are recommended.

Conflict of Interest

None.

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Incidence of Atrial Fibrosis in Non-Valvular Atrial Fibrillation Patients and its Impact on Recurrence after Pulmonary Vein Antral Isolation

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Abstract

Background: Atrial fibrillation (AF) is the most common sustained arrhythmia; it affects 1%–2% of the general population [1]. Many studies demonstrated an association between atrial fibrosis and AF[2]. There is increasing evidence that even in patients with lone AF; the AF is an arrhythmic manifestation of a structural atrial disease which has been described as fibrotic atrial cardiomyopathy[3]. It is unknown whether the presence of atrial fibrosis has any impact on post pulmonary vein antrum isolation outcome. This study aims to determine the incidence of atrial fibrosis in patients with non-valvular AF and its impact on recurrence after pulmonary vein antrum isolation.

Methods: This study included twenty eight consecutive patients referred for first-time pulmonary vein antrum isolation for the treatment of symptomatic recurrent non-valvular AF not responding to medical treatment, Isolation of the pulmonary veins antra was performed using three dimensional electroanatomical mapping, detailed voltage map was done in the right and left atrium, before ablation and Low-voltage zones were identified. Follow up of the patients was done for 6 months after the procedure to detect recurrence of AF.

Results: Left atrium fibrosis was present in 6 (21.4%) cases, right atrium fibrosis was present only in 1 (3.6%) case and recurrence of atrial fibrillation after 6 months occurred in 12 (42.9%) cases. AF burden was significantly higher in the recurrence group [50.33 ±19.7 (48) (hour/month)] as compared to no recurrence group [29.5 ± 6.99 (32) (hour/month)] with P-value 0.002 and the incidence of left atrium fibrosis was significantly higher in the recurrence group as compared to no recurrence group with P-value 0.024. The only significant predictors of recurrence were the presence of left atrium fibrosis (OR 10.71, 95% CI 1.05 to 109.78; P=0.046) and AF burden (OR 1.14, 95% CI 1.02 to 1.27; P=0.023). The only significant predictor of the presence of left atrium fibrosis was AF burden (OR 1.06, 95% CI 1.01 to 1.13; P=0.031)

Conclusion: The presence of the atrial fibrosis in the left atrium is an independent predictor of atrial fibrillation recurrence after pulmonary vein antrum isolation after 6 months without left atium substrate modification.

Introduction

Background

Atrial fibrillation (AF) is the most common sustained arrhythmia; it affects 1%–2% of the general population. Many studies demonstrated an association between atrial fibrosis and AF. There is increasing evidence that even in patients with lone AF; the AF is an arrhythmic manifestation of a structural atrial disease which has been described as fibrotic atrial cardiomyopathy. It is unknown whether the presence of atrial fibrosis has any impact on post pulmonary vein antrum isolation outcome.

Purpose of the study

This study aims to determine the incidence of atrial fibrosis in patients with non-valvular AF and its impact on recurrence after pulmonary vein antrum isolation.

Key Words

AF, Atrial Fibrosis, Electrophysiology, Radiofrequency Ablation

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Patients and methods:

This study enrolled 30 patients referred to the cardiology department at Ain Shams University hospitals for first-time pulmonary vein antrum isolation for the treatment of symptomatic paroxysmal non-valvular AF. Of these patients catheter ablation was postponed in 2 patients because of the development of cardiac tamponade during transseptal puncture, thus the 28 patients were included in the study.

All patients included were free of hypertension, diabetes mellitus, coronary artery disease, and cardiomyopathy thus they were defined as having lone AF. Inclusion criteria included patients with symptomatic paroxysmal atrial fibrillation who were younger than sixty years and AF was documented by 12 lead ECG or Holter monitoring.

Exclusion criteria included patients with history of previous pulmonary vein isolation, patients with history of previous cardiac ablation procedures, patients with history of previous cardiac surgery, patients with persistent or permanent AF and patients with valvular heart disease.

After giving informed written consent and approval of the ethical committee, the selected patients were subjected to the

thorough history taking, physical examination electrocardiogram, echocardiogram and transesophageal echocardiography. Oral anticoagulation was discontinued about 3 days before the procedure itself with bridging with enoxaparin 1mg/kg/12h.

Appropriate preparation including at least 6 hours of fasting before the procedure was necessary. All procedures were done under general anesthesia. After proper local anesthesia, two left femoral venous punctures were done for introduction of a quadripolar 6 Fr catheter at His region (landmark for trans-septal puncture) and a decapolar 6Fr steerable catheter in CS. Two right femoral venous punctures were done followed by exchange wiring with 2 long sheaths (Biosense Webster-PREFACE®) 8Fr caliber, which were introduced via 2 separate trans-septal punctures into LA cavity using the Brockenbrough technique. A circular decapolar mapping catheter (Lasso® catheter, Biosense Webster, Inc.; adjustable 15 to 25 mm circumference; 1–2 mm interelectrode spacing) was introduced to the LA via one long sheath and the ablation catheter (EZ Steer® ThermoCool® Nav catheter Biosense Webster, Inc.; tip electrode 3.5 mm, interelectrode spacing 2-5-2 mm) through the other one. 10,000 IU of heparin were given immediately after successful trans-septal punctures followed by continuous infusion of 1000 I.U. per hour, activated clotting time (ACT) measurement was performed every 30 - 40 minutes to maintain it in the range of 300–400 seconds. The Lasso catheter was positioned in every PV ostium to map PVP. Three dimensional Electro-anatomical mapping was done using CARTO® Platform (CARTO-3; Biosense Webster). The CARTO mapping system utilizes a low-level magnetic field delivered from 3 separate coils in a located pad beneath the patient. The magnetic field strength from each coil is detected by a location sensor embedded proximal to the tip of the specialized mapping catheter. Thus, by integrating each coil's field strength and converting this measurement into a distance, the location sensor (and therefore, catheter tip location) can be triangulated into space. Electro-anatomical voltage mapping: Complete maps of both atria were constructed with recording sites of anatomic relevance and areas of low endocardial voltage. The Atrial shell was created using point by point acquisition. Criteria for an adequate LA shell were ≥100 points that were homogenously distributed to create the entire each atrium with a fill threshold of ≤15[4].

Right and left atrial voltage maps were constructed from the contact bipolar electrograms obtained from the ablation catheter during sinus rhythm. When low voltage zones (LVZ) were apparently identified, we looped the catheters and carefully recorded the voltages to prevent an insufficient wall contact force. For patients in AF at the beginning of the procedure, external direct current cardioversion was performed to restore sinus rhythm and a 15 min interval was taken before mapping. Low-voltage zones were defined as areas with bipolar peak-to-peak voltage amplitudes of < 0.5 mV. The presence of LVZs was defined as that covering >5% of LA body surface area. This cut-off point is equivalent to the minimum grade of LA fibrosis as reported by Mahnkopf et al using DE-MRI evaluation of the LA[5]. Pulmonary vein antrum isolation was performed; RF ablation was jointly performed by a continuous lesion all around the ipsilateral superior and inferior PVs using an open-irrigation catheter creating Wide area of circumferential ablation (WACA). RF ablation was performed with a temperature limit of 40°C, power limit of 25–30W, and infusion rate of 13–20 mL/min with repositioning of the catheter tip every 20 s, but the power was reduced to 20–25W at the LA posterior wall near the oesophagus. The endpoint of the PVAI was entrance and exit block from the PV. All patients remained under in-hospital supervision for 24 hours after the procedure. Oral anticoagulation with Warfarin was initiated in all patients after 4-6 hours of the procedure and also concomitant enoxaparin 1mg/kg/12h until target international normalized ratio (INR) of 2-3 is reached. All patients received the oral anticoagulation for 3 months after the procedure. Anticoagulation strategy after 3 months varied, for patients with CHA2DS2-VASc score of ≥1 long-term warfarin treatment with target INR of 2-3 was continued[6]. A postablation blanking period was observed for 3 months and all patients were kept on the same AAD regimen they were prescribed before the ablation procedure throughout this period. Early recurrences within 3 months were treated with direct current cardioversion, AADs or both to restore sinus rhythm. AADs were discontinued at the end of the blanking period. Follow up for recurrence was done for a duration of 6 months after the procedure by a cardiologist who was blinded to the electro-physiologic procedure results to detect success rate including: history taking as regards recurrence of the symptoms, Surface ECG was taken and repeated after 1 day, 7 days, 1 month, 3 months and 6 months after the procedure or earlier if they developed symptoms consistent with recurrent AF, holter monitoring at 6months or earlier if they developed symptoms consistent with recurrent AF, cases were always asked to record their ECG when symptomatic. Recurrence was defined as any symptomatic or asymptomatic atrial tachyarrhythmia sustained for longer than 30 seconds documented with ECG or Holter monitoring without AAD treatment following the 3 month blanking period[7].

Statistical analysis: Results were analyzed by statistical package for social sciences (SPSS) Data were expressed as mean ± SD and percentage.

Results

The study population included 28 patients referred for first-time pulmonary vein antrum isolation for the treatment of symptomatic paroxysmal AF. Mean age was 42.43 ± 10.42 years; 23 patients were males (82.1%); mean BMI was 29.83 ± 5.13 Kg/m2; mean AF duration was 6.13 ± 6.47 (median 3.5) years; mean AF burden was 38.43 ± 17.19 (median 34) hours/month; AF burden (prior to the

Table 1: Baseline characteristics of the study population

Baseline characteristics		Study sample n = 28
Age (years)		42.43 ± 10.42
Male gender (number, %)		23 (82.1)
BMI (Kg/m2)		29.83 ± 5.13
AF duration (years)		6.13 ± 6.47 (median 3.5)
AF burden prior to the procedure (hours/month)		38.43 ± 17.19 (median 34)
Response to medical treatment (number, %)		4 (14.3)
LA anteroposterior diameter (mm)		39.75 ± 5.77
EF (%)		63.36 ± 4.68
Lateral mitral Annulus E' (cm/s)		10.46 ± 1.91
Diastolic Dysfunction grade	0	19 (67.9)
	1	9 (32.1)

procedure) per month (which was defined as the total number of hours of symptomatic AF episodes per month in the last 3 months). 4 (14.3%) patients responded to medical treatment (they desired drug-free lifestyle) ; mean left atrium antero-posterior diameter was 39.75 ± 5.77 mm; mean ejection fraction 63.36 ± 4.68 %; mean lateral mitral annulus E' was 10.46 ± 1.91 cm/s; as regard diastolic dysfunction 18 (64.3%) patients had no diastolic dysfunction, 9 (32.1%) patients had diastolic dysfunction grade 1 and 1 patient (3.6%) had diastolic dysfunction grade 3. Mean left atrium fibrosis as a percentage of whole left atrium was 10.23 ± 5.51 % [Table 1].

As regards the procedural details 22 (78.6%) of patients underwent PVI only while 6 (21.4%) underwent PVI plus another ablation lesions (2 cases included ablation inside the coronary sinus, 2 cases included ablation of cavo-tricuspid isthmus for counterclockwise typical atrial flutter, 1 case included ablation of right free wall accessory pathway, and 1 case included ablation of Mahaim pathway), Left atrium fibrosis was present in 6 (21.4%) cases, right atrium fibrosis was present only in 1 (3.6%) case and recurrence of atrial fibrillation after 6 months occurred in 12 (42.9%) cases. While there were no major complications during ablation regarding those 28 patients, minimal inguinal hematoma was observed in 1 (3.6%) patient that was relieved conservatively. AF ablation, 'major complication' was defined as a complication which resulted in permanent injury or death, prolonged or required hospitalization' or required intervention for treatment. Two patients were found in AF rhythm the morning of the procedure and they were cardioverted electrically just before 3D mapping. In Comparison between patients with and without AF recurrence: There were no significant differences between the 2 groups regarding age, gender BMI, AF duration (which is the time since the AF diagnosis was made), response to medical treatment, ejection fraction, left atrium size, lateral mitral annulus E' wave, diastolic dysfunction grade, ablation strategy and the presence of right atrium fibrosis [Table 2].

Table 2: Comparison between patients with and without recurrence

Variable		Recurrence n=12	No Recurrence n= 16	P-value
Male gender (number)		9	14	0.624
Response to medical treatment (number)		3	1	0.285
Diastolic Dysfunction grade (number)	0	8	10	0.431
	1	3	6	
	3	1	0	
Strategy (number)	PVI	8	14	0.354
	PVI and other ablation lesions	4	2	
LA fibrosis (number)		5	1	0.024
RA fibrosis (number)		1	0	0.429

However, AF burden was significantly higher in the recurrence group [50.33 ±19.7 (48) (hour/month)] as compared to no recurrence group [29.5 ± 6.99 (32) (hour/month)] with P-value 0.002 and the incidence of left atrium fibrosis was significantly higher in the recurrence group as compared to no recurrence group with P-value 0.024 [Figure 1].

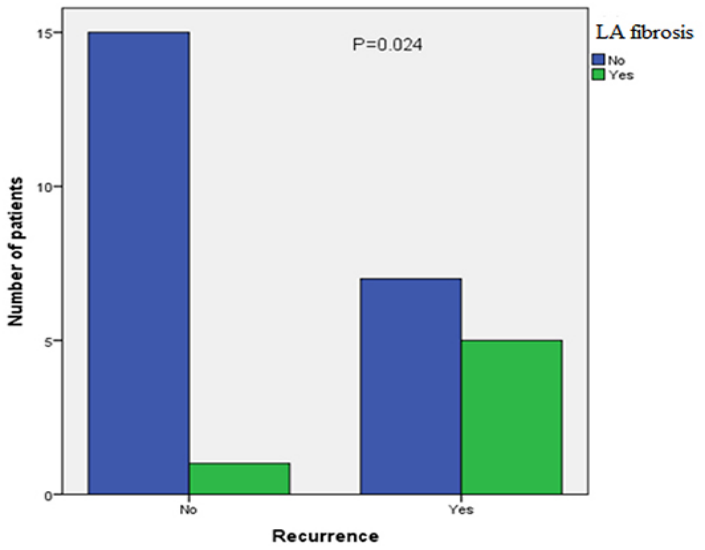

Figure 1: Recurrence of AF after ablation was significantly higher in the presence of left atrium fibrosis with P-value 0.024.

Univariate logistic regression analysis was used to identify variables predicting AF recurrence after 6 months. Analyzed variables included presence of left atrium fibrosis, AF duration, AF burden, left atrium size, age, gender, BMI, ejection fraction, lateral mitral annulus E' wave, procedure strategy and the response to medical treatment. The only significant predictors of recurrence were the presence of left atrium fibrosis (OR 10.71, 95% CI 1.05 to 109.78; P=0.046) and AF burden (OR 1.14, 95% CI 1.02 to 1.27; P=0.023). Univariate logistic regression analysis was used to identify variables predicting the presence of left atrium fibrosis. Analyzed variables included age, gender, BMI, response to medical treatment, AF duration, AF burden, left atrium size, ejection fraction, lateral mitral annulus E' wave. The only significant predictor of the presence of left atrium fibrosis was AF burden (OR 1.06, 95% CI 1.01 to 1.13; P=0.031). No multivariate analysis was done.

Discussion

Our study included 28 patients referred for first-time pulmonary vein antrum isolation for the treatment of symptomatic paroxysmal lone AF, there were no significant differences regarding the Baseline Clinical characteristics of the whole study sample. Recurrence of atrial fibrillation after 6 months occurred in 12 (42.9%). Left atrium fibrosis was present in 6 (21.4%) cases; right atrium fibrosis was present only in 1 (3.6%) case. AF burden was significantly higher in the recurrence group [50.33 ±19.7 (48) (hour/month)] as compared to no recurrence group [29.5 ± 6.99 (32) (hour/month)] with P-value 0.002. The incidence of left atrium fibrosis was significantly higher in the recurrence group as compared to no recurrence group with P-value 0.024.Univariate analyses showed that the only significant predictors of recurrence were the presence of left atrium fibrosis (OR 10.71, 95% CI 1.05 to 109.78; P=0.046) and AF burden (OR 1.14, 95% CI 1.02 to 1.27; P=0.023) and The only significant predictor of the presence of LA fibrosis was AF burden (OR 1.06, 95% CI 1.01 to 1.13; P=0.031). The idea that LA fibrosis was associated with recurrence after AF ablation can be explained by: (1) a LVZ may aggravate an interatrial conduction delay, resulting in the formation of circuits for reentry and thus promote AF perpetuation and (2) a LVZ may act as for the occurrence of non-PV ectopic sites. In 2015 Canpolat et al study showed that LA fibrosis was present in65.9%

patients with lone paroxysmal AF with a median enhancement of 5% of the LA surface area. After cyoablation 78.1% of patients remained free of AF recurrence. Plasma TGF-β1 level (P = 0.001) was found to be the predictor of the extent of LA fibrosis. Multivariate Cox regression analysis pointed out that the extent of LA fibrosis (HR: 1.127, P = 0.007) and early AF recurrence (HR: 1.442, P = 0.011) were the independent predictors of AF recurrence in late follow-up. They concluded that higher levels of TGF-β1 are associated with more extensive LA fibrosis and extent of LA fibrosis predict recurrences in patients undergoing cryoablation for lone AF [8]. In 2014 Yamaguchi et al demonstrated LVZs in 32% of AF patients. During 24±7 months of follow-up 63% with LVZs and 19% without had AF recurrences off antiarrhythmic drugs (log-rank P < 0.001). A multivariate logistic regression analysis revealed that LVZ and ATP-induced reconnection were significant predictors of recurrence[9].

Conclusions

The presence of the left atrial fibrosis is an independent predictor of atrial fibrillation recurrence after pulmonary vein antrum isolation after 6 months without LA substrate modification.

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Two Year, Single Center Clinical Outcome After Catheter Ablation For Paroxysmal Atrial Fibrillation Guided by Lesion Index

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Abstract

Background: This study describes the use of lesion index (LSI) as a direct measure to assess the adequacy of ablation lesion formation with force-sensing catheters in ablation of paroxysmal atrial fibrillation (PAF). LSI is calculated by the formula:LSI = CF (g) ×Current (mA) ×Time (sec).

Methods: Fifty consecutive patients with PAF underwent pulmonary vein (PV) isolation using a catheter dragging technique and targeting different LSI values in different anatomical areas.A force-sensing ablation catheter was used to continuously measure contact force (CF) and guide radiofrequency ablation (RF) lesion formation. Ablation lesions were delivered to achieve an LSI value of 5.0 in posterior locations, 5.5 in anterior locations and 6.0 in the region between the left atrial appendage and left superior pulmonary vein ridge. Force-time Integral (FTI) was not used to evaluate lesion formation.

Results: A single center, retrospective analysis was performed with 196/198 (99%) PVs acutely isolated. The mean procedure time was 134 ± 34 mins and the mean fluoroscopy time was 7.8 ± 3.2 mins. At a mean follow up of two years, 43/50 (86%) of patients were in normal sinus rhythm with no documented recurrences of atrial fibrillation.

Conclusion: LSI can be used to guide the placement of durable lesion formation with RF ablation using CF catheters in patients with PAF.

Introduction

Contact force(CF) sensing catheters have recently been introduced and shown to be an effective tool for increasing the success of ablation for paroxysmal atrial fibrillation (PAF)[1 ,2]. Prior to the introduction of these catheters, indirect measures such as drop in impedance, electrode temperatures, and changes in electrogram morphology were used to assess the adequacy of the lesion delivered[3,4,5,6]. Based primarily on the EFFICAS I and EFFICAS II studies, the primary direct metric that is most commonly used to evaluate adequate lesion formation with radiofrequency (RF) energy is the Force Time Integral (FTI). FTI is a combination of Force and Time[7,8]. FTI, however, does not take into account power delivery. Further more, most studies apply a FTI value of 400 gs to all segments of the left atrium (LA) even though anatomical studies have shown that the tissue thickness varies considerably between different regions in the LA[9,10]. Lesion Index (LSI)is another measure that can be used to guide RF lesion formation[11,12]. LSI is calculated using CF, RF application duration, and RF current. LSI has been used in preclinical studies and in human studies with short term follow up[13,14,15]. Long term clinical outcome data using LSI, however, has not been reported. This single center, retrospective study reviews the two-year clinical outcomes after pulmonary vein isolation (PVI) using a CF sensing 3.5mm irrigated ablation catheter (TactiCath Quartz, Abbott Laboratories, Abbott Park, IL, USA),with lesion formation guided by LSI.

Key Words

Ablation, Atrial Fibrillation, Lesion Index

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Material and Methods

Calculations

FTI is a calculated by the formula: Contact Force (g)× Time (s). The result is expressed in gram seconds (gs) and the result is a linear relationship. LSI, contrastingly, is a non-linear estimate of lesion growth using CF, duration of the lesion and RF current. Use of Current is the main differentiating factor between LSI and FTI. LSI is calculated as a complex weighted, exponential formula assigning different weights to CF, current and time. Each sub component is nonlinear and is expressed as a negative exponential, which accounts for the transition from resistive heating to thermal conduction. LSI is expressed by the formula: LSI = CF (g)×Current (mA)×Time (sec)

All 3 sub components are proportional to $(1\text{-}e^{(-t/\tau)})$. e is the exponential constant, t is time and τ is the time constant. The result is the amount of energy that is delivered[16].

Inclusion and Exclusion

Fifty consecutive patients with symptomatic, drug refractory PAF

that were refractory to Class I or III antiarrhythmic drug (AAD) were admitted for atrial fibrillation (AF) ablation. For all patients, this was their de novo LA ablation procedure. All patients were anticoagulated with a Novel Oral Anticoagulant (NOAC) or therapeutic warfarin, for four weeks prior to the ablation. In addition, all patients that were in AF at the time of ablation underwent a transesophageal echo prior to the case to evaluate for thrombus. A preprocedural CT scan was performed to evaluate the pulmonary vein (PV) and left atrial anatomy. Exclusion criteria included persistent atrial fibrillation (pAF), history of prior catheter or surgical ablation of the LA, presence of a left atrial thrombus or contraindications to oral anticoagulation, myocardial infarction within three months, and severe pulmonary disease.

Intraprocedural Care

Patients were brought into the cardiac electrophysiology laboratory in a fasting state. Antiarrhythmic medications were discontinued at least 48 hours prior to the procedure. Discontinuation of anticoagulation was at the discretion of the operator. All procedures were performed under general anesthesia. Intracardiac echo was employed for imaging for transseptal access. Heparin was infused to achieve an activated clotting time (ACT) of greater than 300 seconds prior to accessing the LA. A continuous infusion of heparin was employed to maintain the ACT between 300s and 350s. A decapolar coronary sinus (CS) catheter (LiveWire, St. Jude Medical, St. Paul, MN, USA) was advanced into the CS and shadowed to maintain a stable reference throughout the case. Two separate transseptal punctures were performed. Two sheaths, a fixed sheath (Daig SL-1, Abbott Laboratories, Abbott Park, IL, USA) and a steerable transseptal sheath (Agilis, Abbott Laboratories, Abbott Park, IL, USA) were inserted into the LA.

Using the impedance based electroanatomic 3D mapping system (Ensite Velocity, Abbott Laboratories, Abbott Park, IL, USA) geometry of the LA and PVswere acquired using a circular mapping catheter (Reflexion Spiral, Abbott Laboratories, Abbott Park, IL, USA). This geometry was displayed along with the anatomy from the CT that was acquired prior to the ablation. An esophageal temperature probe (Level 1 Acoustascope 12 French, Smiths Medical ASD, Inc., St. Paul, MN) was placed and monitored for changes. The esophageal temperature probe was moved inferiorly and superiorly to mirror the location of the ablation catheter. Any increase in temperature was noted and an increase of more than 1.0^{c} led to discontinuation of ablation in that region. Phrenic nerve activity in the right sided veins was evaluated with high output pacing from the Reflexion Spiral in the antrum of the veins. Ablation lesions were delivered via an Ampere RF generator (Abbott Laboratories, Abbott Park, IL, USA) to achieve energy up to 25-35W with a maximum temperature of 42C in each location. Lesions in the posterior LA were limited to 25-30W while lesions in the anterior wall were delivered at 35W. A wide area, antral ablation lesion set was delivered. Lesions were confined to isolation of the PVs. Additional ablation lesions such as a roof line, mitral isthmus line, Complex Fractionated Atrial Electrogram (CFAE), substrate mapping and right atrial cavotricuspid isthmus line were not performed in the study group. At the completion of the ablation, entrance and exit block was demonstrated with all pulmonary veins. In addition, Adenosine (6-18mg) was infused to evaluate PV activity. If there was an increase in PV activity associated with adenosine, further ablation lesions were delivered in the target sites. Adenosine testing was repeated until there was no further activity. At the completion of the case, all patients were in sinus rhythm.

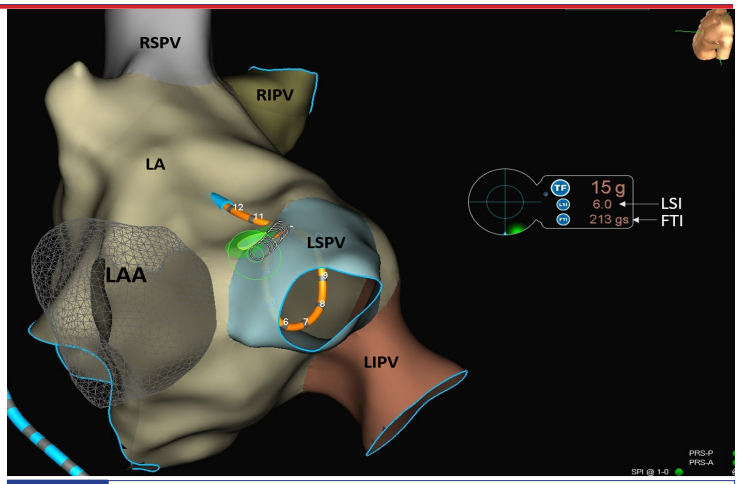

Figure 1: Left Anterolateral view of the Left Atrium(LA). The ablation catheter is contacting the tissue between the Left atrial appendage(LAA) and the Left superior pulmonary vein(LSPV). In this location,an ablation lesion with an LSI value of 6.0 delivered.Contact Force(TF), Lesion Index (LI), Force Time Integral (FTI), Left inferior pulmonary vein (LIPV), Right superior pulmonary vein (RSPV), Right inferior pulmonmary vein(RIPV).

LSI

Based on prior pre-clinical and clinical studies, the lesion index (LSI) was used to guide the duration of each ablation lesion[11-15]. An LSI value of 5.0 was targeted in posterior locations and 5.5 in anterior locations. A higher value of 6.0 was targeted aroundleft atrial appendage (LAA) – left superiorpulmonary vein (LSPV) ridgebecause of increased thickness of the tissue in this area[17].[Figure 1] and [Figure 2]. When the LSI value was achieved, the catheter was moved to the next location. The majority of lesions were delivered with a continuous drag method. In areas where catheter stability was difficult, focal lesions were placed without dragging. The value for LSI was recalculated with every new catheter location. Lesions were delivered with a minimum CF of 10gm and a maximum CF of 40gm. If the CF was out of range or the lesions were not contiguous, the

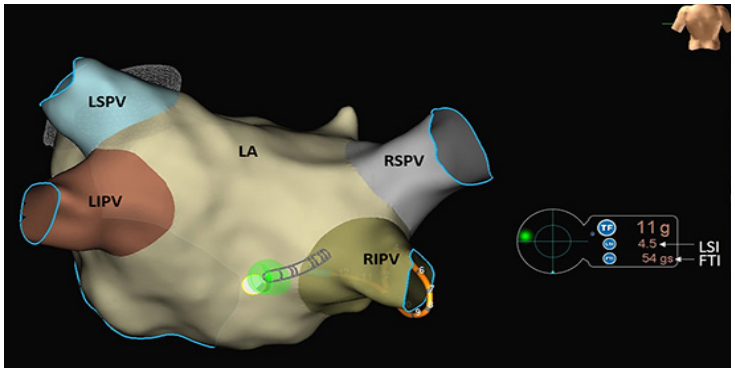

Figure 2: Posterior view of the Left Atrium (LA). The ablation catheter is contacting the issue on the posterior wall. In this loacation, anablation lesion with an LSI of 4.5 was delivered enroute to a total LSI value of 5.0.Contact Force (TF), Lesion Index (LI), Force Time Integral (FTI), Leftinferior pulmonary vein(LIPV), Right superior pulmonary vein (RSPV), Right inferior pulmonmary vein (RIPV).

catheter position was adjusted until the CF was in range. FTI data was not used for lesion evaluation.

Post Procedural Care

All patients were observed overnight and discharged home the next day. All antiarrhythmic medications were discontinued by the end of the three month blanking period. After the three month blanking period was completed, all patients wore a two week continuous monitor capable of detection of asymptomatic episodes of AF. In accordance with the Heart Rhythm Society (HRS) guidelines, all patients were followed for two yearswith ECGs and Holter monitors for documentation of any symptomatic episodes[18]. Anticoagulation was continued at least three months and then guided by the individual patient's CHA_2DS_2-VASc score.

End Points

The primary end point was AF recurrence, defined as a documented episode of AF >30 seconds, either symptomatic or asymptomatic on an event monitor or an ECG. Secondary endpoints were procedural related complications such as pericardial effusion with tamponade physiology, cerebral embolism, groin hematomas, pericarditis and atrioesophageal fistula formation.

Table 1: Patient characteristics

DATA	RESULTS Study Cohort
Age	61±9
Male	34 (79)
LVEF	13 (30)
LA Size	2 (4.7)
CHA_2DS_2-VASC Score	2 (4.7)
DM	4 (8%)
HTN	14 (28%)
CAD	10 (20%)
CHF	1 (2%)
Flouroscopy Time (mins)	7.8 (±3.1)
Total Procedure Time (mins)	134 (±35)

Results

A total of 50 patients were enrolled (43 men and 7 women,mean age 60+8.7, LA Volume 29.3+9.5mL). 14 (28%) had hypertension, 10 (20%) with stable coronary artery disease, 4 (8%) with diabetes mellitus. The meanCHA_2DS_2-VASc score was 0.9 (±1.0).[Table 1].

Ablation Results

In this cohort of 50 patients, 198 individual PVs were evaluated (49 RSPV, 49RIPV's, 1 common right sided vein, 49 LSPV's, 49LIPV's, 1left common vein). A total of 196 of 198 veins were acutely isolated using the LSI value to determine lesion placement. 2/198PVs were not isolated and were both LSPVs. The mean procedure time was 134 + 34 mins and the mean fluoroscopy time was 7.8+3.2 mins. LSI did not affect the overall procedure time of 130 mins which is in line with previously reported trials of ablation of PAF. The fluoroscopy time is also similar to what has been described[19].

Clinical Follow Up

At the one year follow up period, 90% (45/50) patients were in normal rhythm. At the end of the two year follow up period, 86% (43/50) of patients were in normal rhythm with no documented recurrences of AF. The two patients that had pulmonary veins that were not isolated did not have recurrences of atrial fibrillation.

Of the seven patients that did have recurrence of AF, five chose to undergo a repeat ablation procedure. Of those five patients, four had vein reconnection in the anterior portion between the superior portion of the LAA and the LSPV. The fifth patient had the recurrent focus in the region between the LAA and the LIPV. All five patients PVs were successfully re-isolated during the repeat ablation. Long term follow up for the second procedure with a mean follow up 19+4.7 months shows no recurrence of AF. 2/7 of the patients with recurrent arrhythmias chose medical therapy with antiarrhythmicmedication rather than a repeat ablation procedure[Table 2].

Table 2: Characteristics of Recurrent Patients

Recurrent patient	Months from initial procedure to recurrence	Location of recurrent PV reconnection
1	4	LUPV-LAA
2	11	LUPV-LAA
3	5	LLPV-LAA
4	4	LUPV-LAA
5	27	LUPV-LAA

Complications

A 4.0% (2/50) acute complication rate was observed with both as pericardial effusions with tamponade physiology. Both patients required percutaneous drainage with resolution of the effusion. There were no other complications noted.

Discussion

Lesion Index is a novel measurement that can be used to guide the adequacy of RF ablation lesion formation. LSI is calculated from the variables of current, ablation time and CF. LSI is distinct from FTI in that FTI is calculated by time and CF but does not to take into account current delivery. In animal models, the LSI values correlated strongly with PV isolation success[11]. Initial work in humans has also shown acute success in isolation of PVs. Similar to LSI, Ablation Index (AI) has also recently been introduced as a potential value to measure lesion formation[20]. This is the first study, to our knowledge, that takes LSI into account to describe clinical outcomes in ablation of PAF. This retrospective, single center study shows that LSI can be used clinically to evaluate the adequacy of lesion formation with ablation of PAF.

Use of FTI to guide ablation lesion formation is the most commonly described measure of lesion formation in RF ablation for PVI. FTI, however, has limitations in its clinical utility to guide ablation lesion formation. The EFFICAS I trial showed minimum values that were predictive of PV reconnection. Subsequently, in EFFICAS II, the value was used to guide ablation therapy. Even with this result, approximately 37.5% of patients were found to have reconnected PVs. One of the potential limitations of FTI is that it does not take into account the heterogeneity of the thickness of left atrial tissue[17,21]. Atrial tissue in the anterior and roof segments of the LAhave been shown to be thicker and may require more than 400gs

to achieve a full thickness ablation lesion. Contrastingly, atrial tissue in the posterior wall is thinner and may require significantly less than 400gs to achieve a full thickness ablation lesion. Applying an arbitrarily uniform value across all segments of the LA, in particular, the posterior wall, can lead to RF energy reaching extracardiac locations or not achieving a full thickness lesion.

Another area in the LA where the FTI may fall short in determining the lesion placement is in the LAA-LSPV ridge and the posterior wall. The LAA-LSPV ridge location is an area with thick tissue that is difficult to ablate because of catheter stability. Applying a uniform value of 400 gs to a thick region such as this ridge may not lead to a full thickness lesion. By aiming for a higher LSI of 6.0, in this location, a more durable ablation lesion may be achieved. In our study, of the five recurrent patients that had repeat procedures, the most common area of recurrence was the superior portion of the LAA-LSPV ridge. This suggests that a LSI value even greater than 6.0 may be necessary to achieve a durable lesion in this area. However, in the posterior wall of the LA, power is frequently titrated down because of thinner tissue and the proximity of the esophagus. An adequate LSI on the posterior wall can be achieved with a lower power setting and longer ablation time.

Our method of adjusting the LSI with the anatomical location takes these differences into account. For instance (assume, system impedance is 100 ohms)in scenario A, a lesion at 10 grams for 40 seconds achieves an FTI of 400gs. In scenario B, a lesion with 20 grams for 20 seconds also achieves an FTI of 400 gs. If the power delivered in scenario A is 35 Watts (591.6 mA), the lesion created likely is going to be deeper than if power delivered, in scenario B, is 15 Watts (387.3 mA). FTI will not show the difference in these scenarios, as both will have a value of 400gs. LSI, however, will show a difference (since the current is factored in) as the value will be greater in scenario A rather than scenario B.

Additionally, FTI represents the CF accumulated over time; no electrophysiological parameters are taken into account (such as system impedance or RF power delivered). Further, FTI is a bilinear function of CF and time. Consider the case where the CF is fixed during ablation; FTI will increase linearly throughout the entire duration of ablation. It is well-established that lesion growth does not grow linearly, but rather asymptotically (often modeled as a concave exponential function, such as "1 – e (-x)")[22]. In addition to the CF and time, LSI also includes the electrophysiological parameter (current) which can account for patient-dependent factors (such as impedance). The structure of the LSI formula also accounts for the asymptotic behavior of lesion formation.

Finally, the additional component of current delivered in the LSI equation may lead to a more durable ablation lesion and to increase in the clinical success rates at two years. In this retrospective review of a cohort of 50 patients, 86% (43/50) of the patients were in normal rhythm with a mean of two years follow up. This result is higher than previously reported with contact force catheters where the lesion formation was guided by the FTI alone.

Limitataions

The main limitation of this study is that it is a single center, retrospective study with a limited number of patients. In addition, an age and gender match control was not performed. Further studies examining the use of LSI from a prospective method with multiple centers are likely to add additional knowledge to this subject matter. In addition, FTI data was not used for lesion formation so we are unable to correlate the LSI to FTI. Future work should be done to correlate the clinical results of FTI versus LSI in lesion formation.

Conclusion

LSI can guide the duration of the lesion at each ablation location. Based on the location within the LA, the target LSI number will vary. The two-year outcomes, when the LSI is reached at each location, are excellent.

Conflict Of Interest

Drs. Sundaram and Choe are on the speaker's bureau for Abbott Laboratories. In addition, Drs. Sundaram and Choe have received a research grant from Abbott Laboratories, Asia Division to study the genetic basis of Brugada Syndrome in Cambodia. This conflict is not relevant to the article. C. Boorman, N. Mullins, A. Davies and A. Stucky receive salary support from Abbott Laboratories.

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Risk Stratification of an Accessory Pathway Using Isoproterenol after Cardiac Arrest

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Abstract

A 43-year-old man presented after ventricular fibrillation cardiac arrest with evidence of pre-excited atrial fibrillation. Electrophysiology study with guideline-directed testing demonstrated a low risk accessory pathway effective refractory period, which became high-risk with isoproterenol infusion. This case represents a challenging scenario wherein a high-risk pathway may be misclassified using the currently indicated methods of risk stratification.

Case Report

A 43-year-old man with no past medical history presented after out-of-hospital cardiac arrest. The initial rhythm was ventricular fibrillation (VF). The patient was defibrillated and found to be in pre-excited atrial fibrillation (AF); he subsequently underwent direct current cardioversion. The resting electrocardiogram demonstrated sinus rhythm with pre-excitation and no acute ischemic changes.

The patient underwent electrophysiological study (EPS) which revealed an accessory pathway effective refractory period (ERP) of 290ms. When decremental pacing was performed from the atrium, the accessory pathway had 1:1atrio-ventricular conductionat 230ms (see figure). The accessory pathway ERP was 280ms with isoproterenol infusion, and there was 1:1 atrio-ventricular conduction at 200ms with atrial burst pacing (see figure). Atrial fibrillation could not be induced with or without isoproterenol infusion. The accessory pathway was successfully ablated.

Discussion

The shortest R-R interval during AF is considered the best indicator of a high risk accessory pathway due to the fact it reproduces the clinical situation that would lead one to develop VF[1]. It has been demonstrated that the accessory pathway ERP is strongly correlated with thes hortest pre-excited R-R interval (SPERRI) and also with the mean R-R interval during AF[1]. Isoproteronol can be used during EPS as a surrogate of adrenergic stimulation by shortening the SPERRI in patients with WPW. However, the routine use of isoproterenol in risk stratification of accessory pathways is not discussed in the current guidelines, and there is limited data on the significance of a SPERRI < 250 ms with isoproterenol infusion and the risk of sudden cardiac death [2]. There are few case reports of high-risk accessory pathways (SPERRI < 250 ms) being unmasked by isoproterenol infusion.

Our patient did not demonstrate a high risk accessory pathway ERP on or off isoproterenol. However, AV conduction over the accessory pathway improved on isoproterenol from 230ms to 200ms, suggesting a very high risk accessory pathway.

In this particular case, the presentation of ventricular fibrillation with pre-excited atrial fibrillation provided relative certainty regarding the high-risk nature of the accessory pathway. However, had this patient presented for routine EPS with current guideline-based risk stratification, the accessory pathway would have been considered low risk[3]. Atrial fibrillation could not be induced during EPS, further limiting the ability to accurately assess the ERP of the accessory pathway. The challenge presented by this case is the potential for misclassifying high-risk pathways using the currently indicated methods of risk stratification.

Key Words

Wolff-Parkinson White Syndrome, Cardiac Arrest, Electrophysiology Study, Risk Stratification

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Conflicts of interest

Vidal Essebag receives honoraria from St. Jude Medical, Medtronic Inc, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer pharmaceuticals.

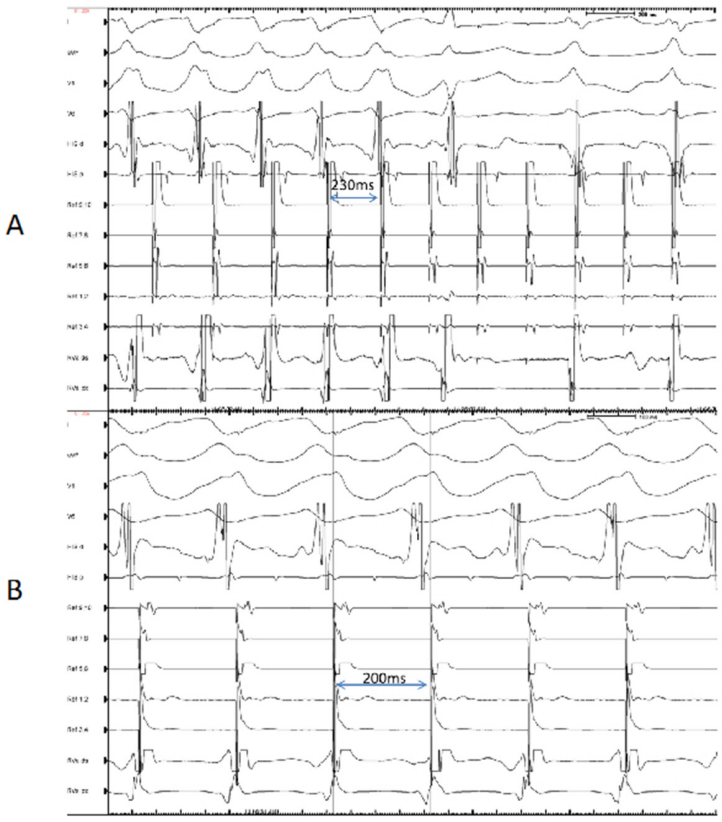

Figure 1: **Maximum 1:1 atrio-ventricular conduction through the accessory pathway with atrial pacing at baseline (A) and with isoproterenol infusion (B)**

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Subxiphoid Hybrid Approach for Epicardial/Endocardial Ablation and LAA Exclusion in Patients with Persistent and Longstanding Atrial Fibrillation

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Abstract

Two patients with long-standing atrial fibrillation (AF) refractory to medical management and with prior pulmonary vein isolation underwent a new hybrid epicardial/endocardial subxyphoid approach for AF ablation and left atrial appendage (LAA) ligation. Pulmonary vein and LA posterior wall isolation, as well as LAA exclusion were achieved in both patients. There were no procedural complications. Both patients remain in sinus rhythm. Both patients are off antiarrhythmic medications.

Introduction

Pulmonary vein isolation (PVI) is a viable alternative for the treatment of paroxysmal atrial fibrillation (AF) and is associated with a high rate of success[1]. However, outcomes for treating persistent and longstanding persistent AF with PVI have been disappointing. Success rates for PVI in patients with persistent and longstanding persistent AF are approximately 45% after one catheter ablation (CA) procedure at 1 year, whereas approximately 65% freedom from AF occurs after multiple procedures[2].

The Cox-Maze III procedure is considered the gold standard for non-pharmacological treatment of AF[1]. It has been associated with a the high rate of maintaining sinus rhythm with a low incidence of stroke in patients with AF [3], but due to the complexity and morbidity of the surgery, few centers perform the operation. Minimally invasive surgical epicardial ablation and hybrid endocardial/epicardial approaches have shown initial promise in maintaining sinus rhythm compared to catheter-based PVI, but are associated with considerably greater number of procedural-related adverse events compared to catheter ablation[4-6].

In this case report, we report on 2 patients with longstanding atrial fibrillation (AF) refractory to medical management and previously failed PVI who underwent a new hybrid subxyphoid epicardial/endocardial approach for AF ablation and left atrial appendage (LAA) ligation.

Key Words

Atrial Fibrillation, Hybrid Epicardial/Endocardial Ablation, LAA Ligation

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Case 1

72 year old woman with a CHADs-VASC score of 4 and long-standing AF refractory to medical management including amiodarone, and a previous PVI underwent a subxyphoid minimally invasive epicardial surgical ablation and LAA closure.

A small subxiphoid incision measuring 6 cm was made. After the xiphoid process was excised and the diaphragm retracted inferiorly with 0 silk suture, the pericardium was entered along the edge of the diaphragm. Increased visualization of the heart within the pericardial cavity was achieved by retraction of the pericardium with stay sutures and a mini thoracotomy retractor with the longer blade on the diaphragmatic surface of the pericardium to inferiorly push the diaphragm down. The pleural space was not entered. The entire inferior surface of the left ventricle and part of the left atrium, the IVC, the right pulmonary veins can be visualized by lifting the heart. Retracting the heart medially with malleable retractor allows for visualization of the left pulmonary veins as well at the LAA.

Isolation of the pulmonary veins were attempted with the Atricure bipolar radiofrequency clamp (AtriCure, Inc, West Chester, OH). Since the Atricure bipolar radiofrequency clamp was designed for a thoracotomy approach, the right angle prevented adequate positioning around the pulmonary veins resulting in partial ablation of the pulmonary veins. Completion of pulmonary vein isolation as well as the posterior left atrium was achieved with the standard Isolator® linear pen probe (AtriCure, Inc, West Chester, OH). Epicardial mapping was performed with the Isolator® linear pen

probe to assure pulmonary vein isolation.

LAA closure was performed with the LARIAT suture delivery device (SentreHeart, Inc, Redwood City, CA). Direct visualization of the LAA was aided by selective lung ventilation, rightward rotation of the bed to lower the right side and rightward traction of the heart with a malleable retractor[Figure 1]. Transesophageal echocardiography (TEE) was used for verification of capture of all lobes of the LAA and complete LAA closure [Figure 1].

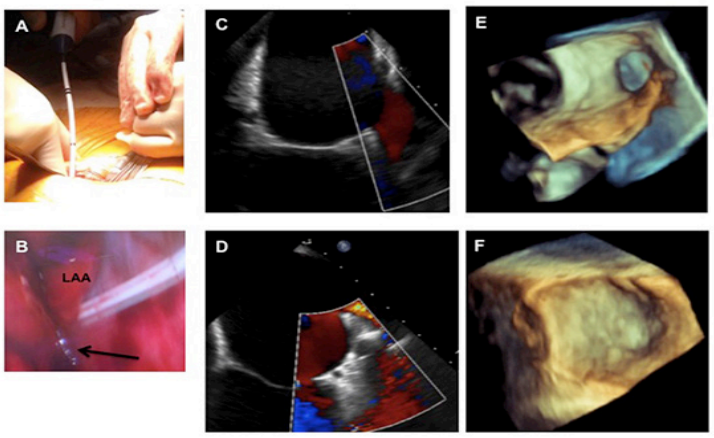

Figure 1: **LAA ligation. Selective lung ventilation, rightward rotation of the table and gentle medial retraction of the heart with a malleable retractor (panel A) allows for direct visualization of the LAA and passage of the LARIAT snare over the LAA (panel B). The arrow highlights the snare around the LAA. TEE is used to assess capture of all the lobes. Panel C and E represent pre-ligation LAA of 2D and 3D TEE images, respectively. 2-D (panel D) and 3-D (panel F) TEE assessment of LAA closure 7 weeks post-LAA ligation verified permanent LAA closure.**

The patient tolerated the procedure without any procedural complications. The patient did develop a pleural effusion on post-operative day 2. During her hospitalization, the patient remained in AF requiring 2 cardioversions to restore sinus rhythm. The patient was discharged in sinus rhythm without any antiarrhythmic medications. The patient remained in sinus rhythm.

The patient underwent an endocardial electrophysiology study 7 weeks after her surgical procedure to assess for pulmonary vein and posterior LA isolation. In the baseline state, there was electrical connection of the right superior (RSPV), right inferior (RIPV), and left superior pulmonary veins (LSPV) to the left atrium. There was also electrical connection of the posterior wall to the left atrium, though the voltage map demonstrated significant scaring and low voltage throughout the posterior wall [Figure 2]. The spiral catheter (St Jude, Minneapolis, MN) was then positioned in the LSPV and ablation was performed at sites demonstrating electrical connection as demonstrated by local atrial electrograms for pulmonary vein isolation. Entrance block occurred in the LSPV with ablation at the anterior medial aspect of the LSPV. Demonstration of exit block was determined by lack of capture of the LA during pacing around the spiral catheter. Continued ablation in regions of normal voltage around the left superior and inferior veins were performed to complete the left sided WACA. Exit block in the left inferior pulmonary vein (LLPV) was demonstrated.

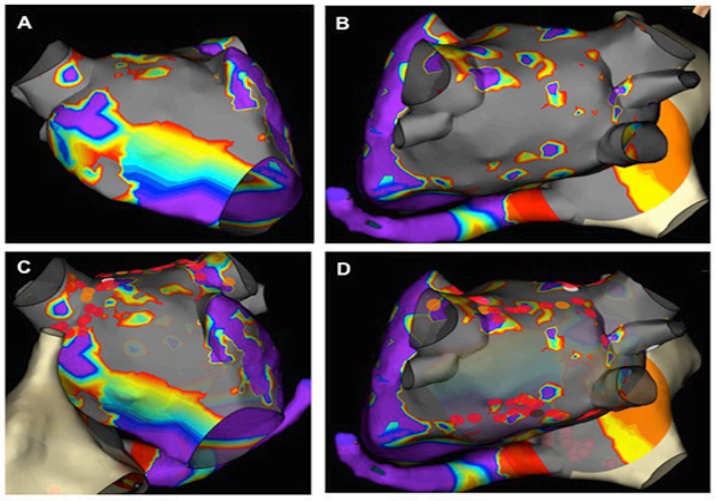

Figure 2: **Voltage maps. Voltage maps prior to endocardial ablation demonstrates areas of residual voltage in the anterior aspect of the LSPV and RSPV (panel A, AP view) and small islands of normal voltage on the posterior aspect of the LA (panel B, PA view). Panel C (AP view) and panel D (PA view) demonstrate the endocardial ablation lesions (2 mm lesions). Red indicates voltage < 0.5 V. Purple indicates voltage >5 V. Gray indicates no signals (ie scar).**

The spiral mapping catheter was next placed in the RSPV. The principle areas of continued conduction were in the anterior aspect of the RSPV near the roof. Entrance block was demonstrated, and pacing around the pulmonary vein also demonstrated exit block. Right-sided WACA line was completed by ablating in areas were there was still residual normal voltage (the anterior portion of the vein had significant voltage still present). Next, the spiral mapping catheter was moved to the RIPV where exit and entrance block of this vein was noted.

The spiral catheter was then positioned in the center of the posterior wall. The posterior wall was isolated by completion of the roof line by ablating in the small islands of normal voltage found in the roof between the right and left superior veins. After completion of the roof line, the inferior posterior wall line from the left inferior vein to the right inferior vein was completed. Completed of this line resulted in the LA posterior wall being electrically isolated. Exit block was then demonstrated by pacing around the spiral catheter in the posterior wall.

Atrial pacing was performed after PVI and posterior LA isolation. Typical cavotricuspid isthmus (CTI) dependent atrial flutter was induced. Patient underwent a successful CTI ablation with demonstration of bidirectional conduction block. Total ablation time was 21 minutes including the right-sided CTI ablation. There were no procedural complications.

The patient has not had symptoms of palpitations and has not taken any anti-arrhythmic drugs since her surgery. Extended monitoring for 4 weeks was performed at 6 and 12 months demonstrating sinus rhythm with no recurrence of AF. A follow up ECG during a visit at 14 months revealed sinus rhythm.

Case 2

71 year-old woman with a CHADs-VASC score of 5, long-standing persistent AF and 2 failed pulmonary vein isolation procedures remained in AF despite continued treatment with amiodarone. She underwent a subxyphoid minimally invasive epicardial surgical ablation and LAA closure as described in case 1. The patient had a successful procedure with demonstration of bilateral pulmonary vein isolation, isolation of the posterior left atrium via epicardial mapping and closure of the LAA with the LARIAT device under direct visualization. There were no procedural complications. The patient had atrial flutter post-operatively with a controlled ventricular rate. The patient subsequently underwent a cardioversion to restore sinus rhythm. The patient remained in sinus rhythm on amiodarone. The planned follow up electrophysiology study was postponed due to the patient requiring an unrelated surgery for her peripheral vascular disease. After the patient's peripheral vascular surgery, amiodarone was discontinued 1 month after her vascular surgery. The patient subsequently developed atrial flutter. Electrophysiology mapping of atrial flutter demonstrated a left sided atrial flutter involving the left pulmonary veins. Entrainment mapping was performed to delineate the circuit and was successfully terminated with radiofrequency catheter ablation. The placement of a 20-pole Spiral catheter was used to confirm entrance and exit block from all 4 PVs and the posterior LA. The patient has remained symptom free and in sinus rhythm off of amiodarone for 8 months, but has continued oral anticoagulation therapy. Extended 3 week monitoring at 6 months post-EPS study revealed predominantly sinus rhythm with rare episodes of asymptomatic atrial fibrillation of less then one-hour duration and constituting less then 6% burden.

Discussion

The subxyphoid epicardial approach was attempted as an alternative to the bilateral thoracic or the transabdominal transdiaphragmatic minimally invasive surgical approach for epicardial AF ablation[5,6]. Although the bilateral thoracic approach has been reported to be more effective then CA for freedom of AF, the bilateral thoracic surgical approach was associated with a significant increase in adverse events compared to CA (23.0% vs 3.2%)[3]. The majority of adverse events associated with the bilateral thoracic approach were major bleeding and pneumothorax. Disadvantages of the transabdominal transdiaphragmatic single port approach is that epicardial LAA closure cannot be performed due to the posterior entry into the pericardial space, and the high rate of complications including those arising from entering the abdominal cavity[6]. The initial attempt of epicardial ablation and LAA exclusion via the subxyphoid approach was found to be feasible and relatively well tolerated.

A subxyphoid approach for the treatment of persistent or longstanding persistent AF allows for epicardial ablation of the posterior aspect of the LA and LAA exclusion with less potential for atrioesophageal fistulas. The addition of LAA exclusion and isolation of the posterior aspect of the LA combined with PVI begins to emulate the Cox-MAZE III procedure which has been shown to be effective in the treatment of persistent AF[7]. The STAR-AF and Chase-AF trial suggests that PVI alone is as effective as PVI plus additional ablation lines or complex atrial fractionated electrograms for the prevention of recurrence of atrial arrhythmias in patients with persistent AF[8,9]. However, these trials were performed in patients with no prior ablation procedure. In patients that have failed PVI, surgical approach including epicardial LAA exclusion and isolation of the posterior LA combined with PVI has greater freedom from recurrence of AF compared to PVI alone[3]. Additionally, LAA ligation is thought to improve freedom from AF recurrence in nonparoxysmal AF due to electrical isolation of the LAA with elimination of potential LAA triggers, LA debulking resulting in electrical remodeling of the LA and allowing for a more complete ablation procedure[10].

In contrast to the transabdominal transdiaphragmatic or bilateral thoracic approach, the subxyphoid approach is familiar to cardiac surgeons who use this approach for pericardial windows. Subxyphoid pericardial access is also familiar to cardiac electrophysiologists who perform epicardial VT ablations or the LARIAT procedure. Direct visualization of the posterior LA and pulmonary veins via a subxyphoid approach or introduction of a space creating device to separate the esophagous from the posterior LA[11] should potentially decrease the potential of atrioesophageal fistulas and allow for a more consistent approach to isolate the posterior LA and pulmonary veins. The potential of creating an atrioesophageal fistula with endocardial ablation has become a deterrent to many cardiac electrophysiologist in creating ablation lesions on the posterior left atrium.

The subxyphoid approach is particularly attractive for a hybrid epicardial/endocardial ablation approach. The surgeon can visualize the posterior aspect of the left atrium and pulmonary veins to perform posterior isolation of the left atrium and linear posterior lines around the pulmonary veins. The cardiac electrophysiologist can perform limited endocardial ablation to complete the isolation of the pulmonary veins and posterior aspect of the left atrium [Figure 3]. The anterior aspect of the LSPV and RSPV, and roof of the LA may be difficult to access epicardially with the current epicardial ablation tools, thus leaving gaps [Figure 3]. However, anterior endocardial ablation of the anterior aspect of the LSPV and RSPV are easily approachable, as well as producing a LA roof line. Producing epicardial ablation lesions from the transverse sinus will allow for an epicardial LA roof line and anterior access to the LSPV and RSVP. A potential epicardial gap would still persist at the transverse recess which would need to be completed via endocardial ablation or via dissection of the transverse recess. Another advantage of the subxyphoid approach is that the LAA can be ligated under direct visualization. If the LAA cannot be visualized, then the LARIAT procedure can be performed by the standard method via the subxyphoid pericardial access and transseptal catherization[12].

Acknowledgements

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Conclusion

This report is the first demonstration of the feasibility of the subxyphoid pericardial access approach for epicardial ablation and LAA ligation and its use as a hybrid epicardial/endocardial approach for persistent and longstanding persistent AF refractory to medications and/or endocardial ablations. As technology advances, the possibility of a complete minimially invasive "MAZE" procedure

via the subyxphoid access approach or a completely percutaneous "MAZE" procedure should be possible.

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Ineffective ICD Shocks for Ventricular Fibrillation in a Patient with a Left Ventricular Assist Device: Continuous Flow During the Electrical Storm

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Abstract

Ventricular arrhythmias are life-threatening and can serve as a precursor to sudden death. They are a common presentation in patients with severely reduced left ventricular (LV) function. The use of an implantable cardioverter defibrillator (ICD) is seen as an acceptable therapy against malignant ventricular arrhythmias. In patients with LV heart failure, a left ventricular assist device (LVAD) can provide pulsatile flow to mimic the cardiac systolic and diastolic function. We report a case of a 38-year-old male with a LVAD who presented to the emergency department due to syncope and frequent ICD discharges. There were documented episodes of ventricular fibrillation and a failed defibrillator threshold test.

Case Presentation

A 38-year-old male was admitted to the emergency department due to syncope and frequent device discharges. The past medical history was significant for dilated cardiomyopathy (DCMP) (LVEF of 25 %) and no reversible cause for the DCMP was found. A previous 12-lead electrocardiogram (ECG) revealed complete left bundle branch block (QRS 145 ms), and a biventricular implantable cardioverter defibrillator (ICD) was implanted at the time. Two years following implantation, his left ventricular (LV) function and functional capacity deteriorated. A left ventricular assist device (LVAD) (Heart Mate III, Abbott, USA) was then implanted and the patient was stable. He was also elected for cardiac transplant and put on the transplant list.

During this indexed episode, the patient witnessed recurrent ICD shocks. Upon arrival of emergency medical services, the patient was found on the floor without consciousness. While in the emergency department (ED), his ECG showed ventricular fibrillation (VF) [Figure 1]. The patient's blood pressure was 95/60 mmHg. An external shock of 200 J (bipolar) converted the patient to sinus rhythm (SR). A follow-up ECG revealed atrial sensed biventricular paced rhythm at 67 beats per minute. The patient was admitted for further investigation. During his stay, he did not experience any further ventricular arrhythmias. A chest X-ray showed the atrial lead in a stable position, however the right ventricular (RV) lead was in the base of the RV. Device interrogation was performed and showed detected episodes of VF and shocks; however, the delivered shocks from the device failed to convert the VF into SR. RV sensing was 11.9 mV and both paced and shock impedances were within normal ranges. A defibrillator threshold test (DFT) was scheduled.

After obtaining consent, the patient was brought into the electrophysiology lab for the DFT. External blood pressure and defibrillator monitoring were present. Under anesthesia, a supported DFT was performed and the ICD delivered[3] shocks. The shocks were ineffective in terminating the VF. External defibrillation was needed to convert the patient to SR. The arterial blood pressure did not change during the recorded VF episode [Figure 2A and 2B]. The patient was informed about his failed DFT and new RV lead implantation was discussed. The patient refused all treatments and requested discharge, which was granted upon his request.

Discussion

Ventricular arrhythmias are a common presentation in patients with severely reduced LV function. ICDs are a widely accepted treatment option to prevent sudden death from malignant ventricular arrhythmias[1],[2]. However, failed, ineffective, or inappropriate ICD discharges are a possibility. Failure to terminate malignant ventricular arrhythmias in patients with ICDs is not a common scenario. Possible reasons for ineffective ICD therapy can be: excessive changes in the sympathetic tone due to epinephrine release which can cause catecholaminergic polymorphic ventricular tachycardia, lead issues (dislocation, inappropriate lead placement or fracture), ICD dysfunction, metabolic decompensation, or structural heart diseases such as hypertrophic cardiomyopathy[3-8]. The Heart Mate III is a wearable LVAD that is designed to supplement the pumping

Key Words
Implantable Cardioverter Defibrillator, Left Ventricular Assist Device, Ventricular Fibrillation.

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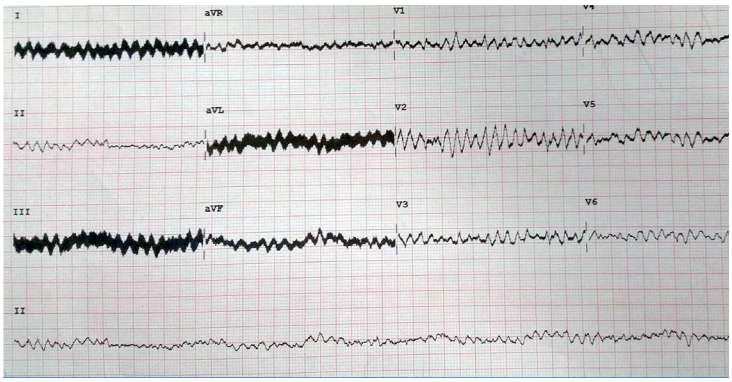

Figure 1: 12-lead electrocardiogram showing ventricular fibrillation.

of the heart through the LV[9]. It serves as the bridge during cardiac transplantation, but it can also assist patients with LV heart failure[10]. The device is attached to the LV and aorta to provide continuous flow. Its unique Full MagLevTM flow technology, based on the CentriMag Pumps, uses magnetic fields to float the device's rotor, creating a contact and friction-free environment[9],[11],[12]. In our patient, the possible explanations for ineffective ICD discharge can be the following:

1. Inappropriate RV lead position:

The RV lead was implanted in the base of the RV and did not cover the entire ventricle. This can be a possible explanation for ineffective ICD shocks. Repositioning of the RV lead was suggested with a follow-up DFT test, however, the patient declined.

2. Magnetic interference between the LVAD and ICD:

ICDs are commonly used in combination with ventricular assist devices, however, their role together has not been fully established[13]. LVADs may have a direct effect on ICDs, causing alteration of lead parameters, ventricular tachycardias, and electromagnetic interference [13].

3. Possible scarring in the LV apex following LVAD implantation causing refractory

VF: This speculation can be proven by a cardiac MRI or 3D mapping. However, the patient refused any further investigations.

Thus far, there have been two reported cases of sustained VF in alert patients with an LVAD and ICD[10],[14]. We add to the growing literature and discuss the possible reasons and explanations for ineffective device treatments in a patient with an LVAD.

Conflict of Interests

None.

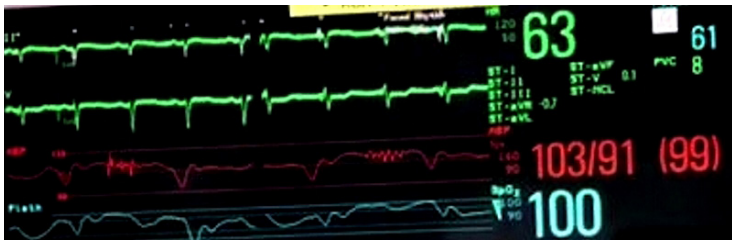

Figure 2A: Live cardiac monitoring during the DFT depicting paced rhythm with simultaneous recording of arterial blood pressure.

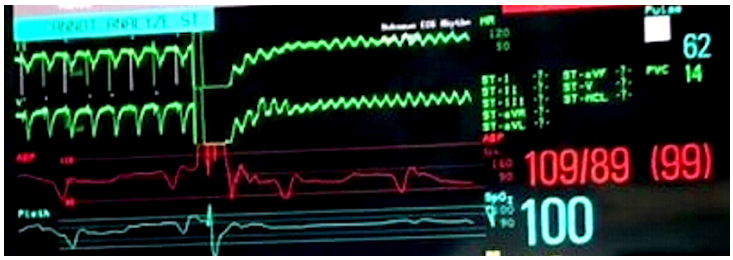

Figure 2B: Induction of VF with shock on T algorithm and arterial blood pressure remained unaffected.

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Management and Disposition of Atrial Fibrillation in the Emergency Department: A Systematic Review

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Abstract

Introduction: Management of atrial fibrillation (AF) and atrial flutter (AFL) in the emergency department (ED) varies greatly, and there are currently no United States guidelines to guide management with regard to patient disposition after ED treatment. The aim of this systematic review was to evaluate the literature for decision aids to guide disposition of patients with AF/AFLin the ED, and assess potential outcomes associated with different management strategies in the ED.

Methods and Results: A systematic review was done using PubMed (MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE, combining the search terms "Atrial Fibrillation", "Atrial Flutter", "Emergency Medicine", "Emergency Service", and "Emergency Treatment". After removal of duplicates, 754 articles were identified. After initial screening of titles and abstracts, 69full text articles were carefully reviewed and 34 articles were ultimately included in the study based on inclusion and exclusion criteria. The articles were grouped into four main categories: decision aids and outcome predictors, electrical cardioversion-based protocols, antiarrhythmic-based protocols, and general management protocols.

Conclusion: This systematic review is the first study to our knowledge to evaluate the optimal management of symptomatic AF/AFLin the ED with a direct impact on ED disposition. There are several viable management strategies that can result in safe discharge from the ED in the right patient population, and decision aids can be utilized to guide selection of appropriate patients for discharge.

Introduction

Atrial fibrillation (AF) is the most common dysrhythmia worldwide, with an estimated prevalence of 2.7 to 6.1 million in the United States (US) alone[1]. The risk for developing AF increases with advancing age, and the US prevalence is predicted to increase to as high as 12.1 million by the year 2030 as the elderly population continues to grow[2]. Along with the increased burden of disease, emergency department (ED) visits for symptomatic AF have continued to rise over the last 25 years, almost doubling from 1993 to 2004[3]. Despite a fairly stable relative rate of hospitalizations, the absolute number of hospitalizations for AF continues to climb as ED visits become more frequent[3]. National incremental healthcare costs of AF in the US are estimated to range from $6 to $26 billion, and a large portion of these expenses are related to inpatient hospitalization [4]. By preventing unnecessary hospital admissions for AF, it could be surmised that both healthcare costs and unwanted complications associated with hospitalization could be significantly reduced. The most recent American Heart Association/American College of Cardiology/Heart and Rhythm Society guidelines for management of AF do not specifically address management in the ED[5]. However, recent guidelines from the Canadian Cardiovascular Society do provide recommendations for ED management of AF, noting that there is increasing evidence that many patients with AF can be safely managed in the ED and discharged to home, without necessitating hospitalization[6]. The aim of our study was to search the existing literature for management strategies and decision aids for triaging ED patients with AF, specifically with a plan for selecting patients appropriate for outpatient management.

Key Words

Atrial Fibrillation, Atrial Flutter, Emergency Medicine, Emergency Service, Emergency Treatment

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Methods

Study Population

We performed a literature search on October 12, 2016 using PubMed (MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE. The searches combined the terms "Atrial Fibrillation", "Atrial Flutter", "Emergency Medicine", "Emergency Service", and "Emergency Treatment". Additional relevant articles that were identified as references for the articles found during the primary search were also included in the review process. Articles published in English were accepted for this review, and non-English language articles were excluded at the title/abstract screening stage. Randomized controlled trials, non-randomized controlled trials, prospective and retrospective cohort studies, case-control studies, and case series were included. Cross-sectional studies, case reports, editorials, letters, comments, abstracts and poster presentations, guidelines, meta-analyses, and review articles were excluded.

Manuscripts selected for this review included: 1) ED management strategies for symptomatic AF or atrial flutter (AFL) directed toward

ED discharge, 2) a focus on the efficacy and/or safety of triaging or management protocols to assist with disposition of patients with AF/AFLin the ED, and 3) evaluation of short term outcomes (< 3 months) of patients with a primary diagnosis of AF/AFLwho were discharged from the ED. Articles that focused on the management of AF/AFL in the ED but without a direct impact on disposition were excluded. Articles that explored past predictors of hospital admission for AF/AFL without relating to patient outcomes were excluded. Articles that only evaluated outcomes more than 3 months after ED discharge were excluded, as we felt short term outcomes were more likely to be related to ED management and discharge. Additionally, articles that primarily focused on acute and long-term anticoagulationfor stroke prophylaxis were excluded.

After the initial database search and removal of duplicates, articles were screened and included or excluded based on title and abstract information. The articles that were included after this initial screening stage were then analyzed using full-text review, and included or excluded based on the previously mentioned inclusion/exclusion criteria. The entire screening process was performed by two independent reviewers (JV, MS)utilizing the Covidence web-based software platform, and conflicts were resolved by consensus with the assistance of a third independent reviewer (AG). The methodology for this systematic review is summarized in [Figure 1].

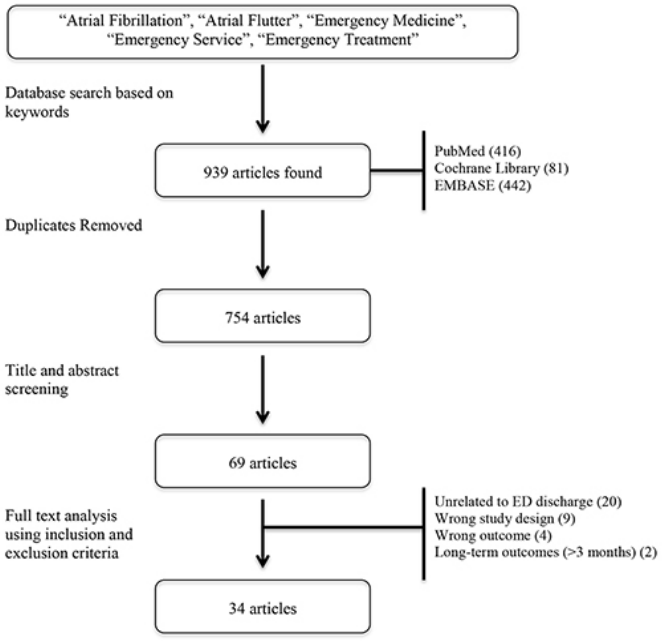

Figure 1: Systematic Review Process

Data extraction was performed individually by the two primary independent reviewers for the studies that were included after full text analysis. Relevant factors from each study were assessed for the final qualitative analysis, including study design, patient population, follow-up period, and interventions and outcomes.

Results

We identified a total of 939 articles (416 from PubMed, 81 from Cochrane Library, and 442 from EMBASE). Duplicates were excluded, resulting in 754 remaining articles. These articles were carefully screened based on information gathered from the titles and abstracts, leaving 69 articles to be analyzed by full text review. Twenty articles were excluded because although they discussed the management of AF/AFLin the ED, they did not specifically address patient disposition from the ED. Nine articles used one of the study designsthat we chose to exclude and 4 had irrelevant patient outcomes for our topic of interest. Finally, 2 articles were excluded because their primary focus was on long-term patient outcomes. This left 34 remaining studies to be included in our review. There were 4 randomized controlled trials, 10 prospective cohort studies, 12 retrospective cohort studies, 6 prospective case series, and 2 retrospective case series. Because our inclusion criteria allowed for some variety in the content of our articles, we grouped the articles into 4 separate categories: decision aids and outcome predictors, electrical cardioversion-based protocols, antiarrhythmic-based protocols, and general management protocols.

Decision Aids and Outcome Predictors

Seven of the articles focused specifically on how to determine which patients with AF/AFLcan be safely discharged from the ED by analyzing short term outcomes and creating novel prediction models and decision aids [Table 1][7-13]. The retrospective analysis done by Mulcahy et al reviewed the charts of all patients who presented to the ED with new-onset AF from 1987 to 1992, all of whom were subsequently admitted to the inpatient ward per hospital policy at that time[7]. Based on the overall hospital courses and interventions required while inpatient, they found that about one-third of these patients did not merit inpatient hospitalization, and 98% of those that did require inpatient care were easily identified while in the ED. RED-AF, a prediction model created by Barrett et al, assigned points for 12 clinical variables in ED patients with AF/AFL and predicted the risk of an adverse event at 30 days based on total points[8]. The initial model had modest predictive discrimination and was later prospectively validated with similar performance as the original cohort[11]. The biggest predictors of increased risk for short-term adverse events were increased age, inadequate ED rate control, dyspnea, smoking, and home beta-blocker use[8]. The AFFORD prediction model for 30-day adverse events was also created by Barrett et al, a few years after RED-AF, and assigned points to 17 different variables for risk stratification[12]. Atzema et al created both a complex as well as a pragmatic clinical decision instrument for risk-stratification, both of which performed well for predicting 30-day all cause mortality[13]. Compared with the complexity of the previous models, the pragmatic model (TrOPs-BAC) includes only 6 variables (positive troponin, other acute ED diagnosis, pulmonary disease, bleeding risk, age 75 years or older, and congestive heart failure) and can easily be memorized for quick reference. Atzema et al performed a large retrospective cohort study to look for factors associated with death within 90 days of an ED discharge after a visit for AF/AFL, and found that having no follow-up care was associated with the highest risk for short-term death (hazard ratio [HR] 2.27)[9]. This group also explored predictors for repeat ED visits for AF/AFL within 2 weeks of an ED discharge, and found that follow-up with a cardiologist or internist was associated with the lowest hazard for repeat visits (HR 0.61)[10].

Electrical Cardioversion-Based Protocols

Seven of the articles primarily analyzed the safety and efficiency

Table 1: Decision Aids

Author/Year	Study Design	No. of Patients	Inclusion Criteria	Intervention	Key Outcome Measures	Results
Mulcahy et al 1996[7]	Retrospective cohort study	229	ED patients with new diagnosis AF	Determination of medical justification of hospitalization for AF	Rate of medically justified admissions ED or hospital complications	1/3 of admitted AF patients did not merit hospitalization 98% of medically justified admissions could be identified in the ED
Barrett et al 2011[8]	Retrospective cohort study	832	ED patients with AF/AFL	Derivation and internal validation of RED-AF prediction model	30-day adverse events	RED-AF had modest predictive discrimination for the primary outcome (c-statistic of 0.67)
Atzema et al 2013 [9]	Retrospective cohort study	12,772	ED patients>65 years old with primary diagnosis AF/AFL	Discharge home from the ED	90-day all-cause mortality	3% death rate within 90-days Significantly increased hazard of death for patients with no outpatient follow-up
Atzema et al 2013 [10]	Retrospective cohort study	12,772	ED patients>65 years old with primary diagnosis AF/AFL	Discharge home from the ED	Return ED visit within 14 days	9% of patients had a return ED visit Patients with specialist outpatient follow-up less likely to return Patients with only family practice outpatient follow-up, high acuity triage score, and history of CHF more likely to return
Barrett et al 2015[11]	Prospective cohort study	497	ED patients with stable AF/AFL	Prospective validation of RED-AF prediction model	30-day adverse events	RED-AF performed similar to the original derivation cohort (c-statistic of 0.65) Clinically relevant threshold score had 96% sensitivity, 19% specificity, PPV 27%, NPV 93%
Barrett et al 2015[12]	Prospective cohort study	497	ED patients with stable AF/AFL	Derivation and internal validation of AFFORD clinical decision aid	30-day adverse events	AFFORD performed moderately well for predicting risk of short-term adverse outcomes (c-statistic of 0.7)
Atzema et al 2015[13]	REtrospective cohort study	3,510	ED patients with primary diagnosis AF	Derivation and validation of complex and pragmatic decision models for disposition of ED patients with AF	30-day all cause mortality	Both models were highly predictive of the outcome (c-statistic 0.87 and 0.81 for complex and pragmatic model, respectively)

AF = atrial fibrillation, AFL = atrial flutter, CHF = congestive heart failure, ED = emergency department, NPV = negative predictive value, PPV = positive predictive value

of direct-current cardioversion (DCCV) as a means to successfully discharge patients home from the ED [Table 2][14-20]. Conversion rates for DCCV were as high as 97% in the prospective cohort study by Jacoby et al, and no lower than 78%, which was the rate observed by Dankner et al[15,17]. In each of these studies, almost all of the patients who converted to normal sinus rhythm (NSR) were discharged home from the ED. Several of the studies noted a small number of minor ED complications with DCCV, primarily related to procedural sedation[14,16,18,19,20]. No major adverse events were observed within 3 months of discharge after ED DCCV in any of the included studies.

Table 2: Electrical cardioversion

Author/Year	Study Design	No. of Patients	Inclusion Criteria	Intervention	Key Outcome Measures	Results
Burton et al 2004[14]	Retrospective cohort study	388	ED patients with stable AF	Elective DCCV Elective CC Rate control only	ED disposition Conversion to NSR ED and 1-week adverse events	86% of all patients discharged home 86% conversation rate with DCCV 28 ED DCCV complications
Jacoby et al 2005[15]	Historically controlled prospective cohort study	60	ED patients with primary diagnosis stable AF/AFL AF duration <48 hours	Elective DCCV Historical controls with rate control only and hospital admission	ED disposition Conversion to NSR Post-discharge adverse events	80% of DCCV patients discharged home 97% conversion rate with DCCV No adverse events noted with telephone follow-up for DCCV patients
Lo et al 2006[16]	Prospective case series	33	ED patients with stable AF AF duration <48 hours	Elective DCCV	ED disposition Conversion to NSR ED and 3-month adverse events	79% of all patients discharged home 91% conversion rate with DCCV No major adverse events at 3 months
Dankner et al 2009[17]	Retrospective cohort study	374	ED patients with stable AF AF duration <48 hours or >48 hours with therapeutic INR	Elective DCCV Elective CC Rate control only	ED disposition Conversion to NSR 1 and 2-week adverse events	53% of DCCV patients discharged home 78% conversion rate with DCCV No definite treatment-related adverse events with DCCV
Scheuermeyer et al 2010[18]	Retrospective case series	400	ED patients with primary diagnosis stable AF/AFL AF/AFLduration <48 hours or >48 hours with therapeutic INR	Elective DCCV	ED disposition Conversion to NSR ED and 30-day adverse events	97% of patients discharged to home 97% conversion rate with DCCV No major 30-day adverse events 4.3% rate of minor procedural complications
Scheuermeyer et al 2011[19]	Retrospective cohort study	122	ED patients with primary diagnosis stable AFL	Elective DCCV Elective CC Spontaneous cardioversion Rate control only No rate or rhythm control	ED disposition Conversion to NSR ED adverse events	93% of DCCV patients discharged home 91% conversion rate with DCCV patients 2 DCCV patients had minor procedural complications
Cristoni et al 2011[20]	Prospective cohort study	322	ED patients with stable AF AF duration <48 hours	ED SOU management (DCCV vs. CC)	ED disposition Conversion to NSR Short-term adverse events	94% of patients discharged from ED in DCCV group vs. 56% in CC group 93% conversion rate in DCCV group vs. 51% in CC group No significant difference in short-term adverse events

AF = atrial fibrillation, AFL = atrial flutter, CC = chemical cardioversion, DCCV = direct current cardioversion, ED = emergency department, INR = international normalized ratio, NSR = normal sinus rhythm, SOU = short observation unit

Table 3: Medical Management

Author/Year	Study Design	No. of Patients	Inclusion Criteria	Intervention	Key Outcome Measures	Results
nnes et al 1997[21]	Randomized controlled trial	41	ED patients with stable AF, <75 years of age AF duration <48 hours	Sequential verapamil-quinidine Sequential digoxin-quinidine	ED disposition Conversion to NSR ED adverse events	63% of VER-Q and 27% of DIG-Q discharged home from ED 84% of VER-Q patients and 45% of DIG-Q patients successfully converted within 6 hours No significant adverse events
Ganau et al 1998[22]	Randomized controlled trial	156	ED patients with stable AF, <80 years of age AF duration <72 hours	IV propafenone IV saline placebo	ED disposition Conversion to NSR ED adverse events	65% of propafenone patients and 20% of placebo patients discharged home from ED 70% of propafenone patients and 17.3% of placebo patients converted within 2 hours 4 patients with minor, transient complications
Ergene et al 1998[23]	Prospective cohort study	50	ED patients with stable AF, <75 years of age AF duration <72 hours	PO propafenone	ED disposition Conversion to NSR Predictors for successful conversion ED adverse events	78% of patients discharged home from ED 78% conversion rate Higher response rate for symptom onset <24 hours 3 patients with severe hypotension responsive to IV fluids
Domanovits et al 2000[24]	Prospective case series	51	ED patients with stable AF/AFL AF duration <48 hours	IV ibutilide with DCCV for non-responders	ED disposition Conversion to NSR ED adverse events	92% of all patients discharged home from ED 75% conversion rate with ibutilide, 100% conversion rate with ibutilide +/- DCCV No major adverse effects
Mountantonakis et al 2006[25]	Prospective case series	36	ED patients with stable AF/AFL AF duration <72 hours	IV ibutilide	ED disposition Conversion to NSR ED adverse events	All patients who converted discharged home from ED 69% conversion rate No major adverse effects
Viktorsdottir et al 2006[26]	Retrospective cohort study	46	ED patients with stable AF/AFL AF duration <7 hours	IV ibutilide Rate control only	ED disposition Conversion to NSR ED adverse events	All patients who converted discharged home from ED 64% conversion rate in ibutilide group vs. 29% in rate control group No adverse effects in ibutilide group
Stiell et al 2007[27]	Retrospective case series	341	ED patients with primary diagnosis stable AF/AFL AF/AFLduration <48 hours	IV procainamide with DCCV for non-responders	ED disposition Conversion to NSR ED adverse events	94.4% discharged home from ED 50% conversion rate with procainamide alone, 91% with procainamide +/- DCCV 10% rate of adverse events, transient hypotension most common
Hirschl et al 2011[28]	Prospective cohort study	376	ED patients with stable AF AF/AFLduration <48 hours	IV flecainide IV ibutilide IV amiodarone IV magnesium IV digoxin IV diltiazem IV digoxin + diltiazem	ED disposition Conversion to NSR ED adverse events	All cardioverted and rate controlled patients discharged home from ED 45% overall conversion rate; flecainide (95%) and ibutilide (75%) had highest success rates 4% adverse event rate, lowest in digoxin and digoxin + diltiazem group
cheuermeyer et al 2013[29]	Retrospective cohort study	259	ED patients with primary diagnosis stable AF	BB CCB	ED disposition ED LOS ED and 30-day adverse events	No significant difference in ED LOS or discharge home from ED for BB vs. CCB (78% and 69%, respectively) No major ED adverse
White et al 2015[30]	Historically controlled prospective cohort study	104	ED patients with primary diagnosis stable AF/AFL AF/AFLduration <48 hours	IV procainamide with DCCV for non-responders Historical controls with standard care	ED disposition Conversion to NSR 30-day adverse events	93% of cohort discharged home from ED vs. 40% of historical controls 94% conversion rate for cohort vs. 56% of historical controls No major adverse events

AF = atrial fibrillation, AFL = atrial flutter, BB = beta blocker, CCB = calcium channel blocker, DCCV = direct current cardioversion, DIG-Q = digoxin plus quinidine, ED= emergency department, IV = intravenous, LOS = length of stay, NSR=normal sinus rhythm, PO = by mouth, VER-Q= verapamil plus quinidine

Notably, hemodynamic instability was an exclusion criterion for all of these studies, so DCCV was done purely on an elective basis. Additionally, 3 of the 7 studies required the onset of AF/AFL to be less than 48 hours prior to ED presentation for study inclusion[15,16,20]. The other 4 studies permitted an earlier onset of symptoms, but the large majority of patients still only had symptoms for 48 hours or less, no fewer than 68% of the cohort in the AFL study done by Scheuermeyer et al[14,17,18,19].

Antiarrhythmic-Based Protocols

Ten of the articles dealt with medical management of AF in the ED, either with chemical cardioversion or rate control alone [Table 3][21-30]. Chemical cardioversion had varying success rates depending on the pharmacologic agent that was chosen. The combinations of verapamil-quinidine and digoxin-quinidine used by Innes et al resulted in 84% and 45% conversion rates to NSR, respectively[21]. Intravenous (IV) and oral (PO) propafenone had 70% and 78% successful conversion rates, respectively[22,23].The use of IV ibutilide resulted in conversion rates ranging from 64% to 76%[24,25,26,28]. IV procainamide was used by Stiell et al and White et al with a 50% and 67% success rate, respectively [27,30]. Hirschl et al compared a variety of different medications, and found that flecainide (95%) and ibutilide (76%) had the highest rates of conversion to NSR [28]. Similar to the DCCV studies, all of these studies required a recent onset of AF/AFL for study inclusion.Only one of the articles in our study evaluated rate control alone with regard to ED discharge, comparing outcomes of those who received beta-blockers vs. calcium channel blockers, finding no significant differences in discharge rates or short-term adverse events[29].

General Management Protocols

NThe final category included ten articles, which either explored the efficacies of several different AF/AFL management strategies with the goal of ED discharge, or used specific protocols designed

to appropriately triage and disposition ED patients with AF/AFL [Table 4][31-40].Michael et al and Vinson et al compared several different ED management strategies, with DCCV being the most successful with regard to conversion to NSR[31,38]. However, 97% and 89% of all patients were discharged to home in Michael and Vinson's groups, respectively, including those who only underwent rate control or observation. Vinson et al observed a 29% rate of spontaneous cardioversion in the ED without any intervention; this rate improved

Table 4: General Management Protocols

Author/Year	Study Design	No. of Patients	Inclusion Criteria	Intervention	Key Outcome Measures	Results
Michael et al 1999[31]	Retrospective cohort study	289	ED patients with primary diagnosis stable AF	Elective DCCV Elective CC SC before or after treatment Rate control only	ED disposition Conversion to NSR ED and 1-week adverse events	97% of all patients discharged home 89% conversion rate for DCCV, 50% for CC, 15% spontaneously converted No adverse events with DCCV, 9% complication rate with CC
Koenig et al 2002[32]	Prospective case series	67	ED patients with stable AF AF duration <48 hours Failed ED cardioversion	EDOU management (rate control, CC, and/or DCCV)	ED disposition Conversion to NSR ED and 1-week adverse events	81% of patients discharged home from ED 82% overall conversion rate No major adverse events
Kim et al 2002[33]	Randomized controlled trial	18	ED patients with primary diagnosis new-onset, stable AF, <75 years old	Accelerated ED pathway Hospital admission	ED disposition ED/hospital LOS ED adverse events	100% conversion rate and discharge home from ED for accelerated pathway Mean LOS was 2.1 days for hospital admission vs. <1 day for accelerated pathway No major adverse events
Zimetbaum et al 2003[34]	Prospective cohort study	446	ED patients with primary diagnosis new-onset, stable AF	ED AF practice guideline Pre-intervention standard care	ED disposition 30-day return visits and adverse events	49% decrease in probability of hospital admission No difference in 30-day return visits or hospitalizations No 30-day strokes or death
Decker et al 2008[35]	Randomized controlled trial	153	ED patients with primary diagnosis stable AF AFduration, <48 hours	EDOU protocol Hospital admission	ED disposition Conversion to NSR or rate control ED, 30-day, and 6-month adverse events	85% of EDOU discharged home from ED 85% conversion rate in EDOU group vs. 73% in hospital admission group No significant difference in short term adverse effects
Stiell et al 2010[36]	Prospective case series	660	ED patients with primary diagnosis stable AF AF/AFL duration, <48 hours	Ottawa Aggressive Protocol	ED disposition Conversion to NSR ED and 1-week adverse events	97% of all patients discharged home from ED 92% successful conversion rate with IV procainamide +/- DCCV No major adverse events
Scheuermeyer et al 2012[37]	Retrospective cohort study	927	ED patients with primary diagnosis stable AF	Elective DCCV Elective CC SC Rate control only	ED disposition Conversion to NSR ED and 30-day adverse events	85% of patients discharged home 46% conversion rate to NSR 3% rate of adverse events in ED, 0.8% rate of stroke or death at 30 days
Vinson et al 2012[38]	Prospective cohort study	206	ED patients with primary diagnosis stable AFduration, <48 hours	Elective DCCV Elective CC SC Rate control only	ED disposition Conversion to NSR ED and 30-day adverse events	89% of patients discharged home 96% success rate for attempted cardioversion Rate of spontaneous conversion to NSR was 29% in ED, 69% within 48 hours of discharge home No major ED adverse events, 1% rate of stroke and no deaths at 30 days
Elmouchi et al 2014[39]	Prospective case series	100	AF clinic patients seen in follow-up after discharge home from ED visit for AF	Spectrum Health AF Protocol with AF clinic follow-up	90-day return ED visits or hospitalization 90-day mortality and TE events	10 AF-related return ED visits, 3 AF-related hospitalizations within 90 days No deaths or TE events at 90 days
Ptaszek et al 2016[40]	Prospective cohort study	359	ED patients with stable AF	AF treatment pathway Standard care	ED disposition Repeat visits or hospitalization	84% of AF pathway patients vs. 20% of controls discharged home from ED No significant difference in short-term readmissions

AF = atrial fibrillation, AFL = atrial flutter,CC = chemical cardioversion, DCCV = direct current cardioversion, ED= emergency department, EDOU = emergency department observation unit, IV = intravenous, LOS = length of stay, NSR = normal sinus rhythm, SC = spontaneous cardioversion, TE = thromboembolic

to 69% within 48 hours of discharge to home[38]. Scheuermeyer et al looked at outcomes of ED patients with symptomatic AF and no other underlying medical cause who received a similar variety of interventions, with 85% of patients discharged home from the ED and a 0.8% rate of stroke or death at 30 days[37]. Koenig et al observed an 81% discharge rate with no major adverse events after utilization of an ED observation unit for those who did not respond initially to ED management[32]. Stiell et al used a case series to evaluate the Ottawa Aggressive Protocol, which consisted of administration of IV procainamide followed by DCCV for those who did not convert to NSR initially, and showed that 97% of patients were discharged home from the ED without any major adverse events[36]. Kim et al and Decker et al both randomized patients to undergo protocols geared toward ED discharge vs. hospital admission, and found no significant difference in short-term adverse events[33,35]. Zimetbaum et al and Ptaszek et al compared their AF protocols to standard ED care, and found a 49% and 80% decreased probability of hospital admission, respectively, with no significant differences in short-term adverse events or hospitalizations[34,40]. Elmouchi et al created the Spectrum Health ED AF protocol, which had different treatment algorithms based on time of AF onset, and required close follow-up in an AF-specific clinic[39]. Out of 100 included patients, there were only 10 repeat ED visits and 3 hospitalizations for AF within 90 days, with no deaths or thromboembolic events.

Discussion

To our knowledge, this is the first systematic review to evaluate the optimal management of AF/AFL in the ED, specifically with regard

to appropriate triaging and disposition. Based on the results of the included articles, there are multiple, varying strategies to approach management as well as risk stratification. Moreover, our review suggests that by using these strategies, most patients can be safely discharged from the ED and managed successfully in the outpatient setting. Based on our review, we concluded three major findings: 1) decision aids and prediction models can be useful for determining ED disposition, 2) electrical cardioversion is more successful than medical management in converting to NSR, and 3) conversion to NSR is not required to allow for safe ED discharge.

Deciding which patients are safe to discharge from the ED and which require inpatient admission is not always straightforward, but one of our primary findings was that using prediction models can be helpful for stratifying patients. The RED-AF and AFFORD clinical tools both had modest predictive discrimination for their outcomes of interest, and the decision instruments created by Atzema et al were highly predictive of 30-day all cause mortality[8,11,12,13].Unlike many of the articles in this review, these decision aids did not exclude patients with other underlying acute medical conditions requiring hospitalization,which could broaden their applicability.Each of these studies was done at a single academic institution, and further validation in a variety of ED settings would strengthen the case for widespread use of these decision instruments. Regardless of risk stratification, transitions of care are an important aspect of acute AF/AFL management. Atzema et al demonstrated in 2 different articles that patients without adequate short-term follow-up had worse outcomes, reinforcing that close outpatient follow-up is important to ensure a safe ED discharge [9,10].

Electrical cardioversion was largely very successful in the articles we reviewed and helped with discharge from the ED. Several of the studies in the DCCV group directly compared electrical and chemical cardioversion, and found DCCV to have significantly higher successful conversion rates[14,17,19,20]. Although none of the studies in the antiarrhythmic group directly compared chemical cardioversion to DCCV, all of the pharmacologic agents had lower conversion rates than the results seen in the DCCV studies. A few of the chemical cardioversion studies used DCCV as an adjunct therapy for those who did not initially respond to the pharmacologic agents, with subsequent improvement of successful cardioversion[24,27,30]. In each study in the DCCV and antiarrhythmic groups, almost all patients who converted to NSR were discharged home from the ED. Importantly, with either DCCV or chemical cardioversion, it was critical to know the exact onset of the AF/AFL episode to ensure that the onset was less than 48 hours duration. In many cases this cannot be reliably determined and would thus warrant a transesophageal echocardiogram. This limits the utility of this strategy in many patients. In addition, in these patients with new onset AF/AFL, it is possible that many will spontaneously convert without an intervention in the ED, as a large proportion will likely have paroxysmal AF/AFL.

The final group of articles employed a combination of rate control, DCCV, chemical cardioversion, and observation alone, most by using implemented pathways and protocols with the aim of ED discharge when possible. These studies demonstrated a high success rate of ED discharge, regardless of the type of acute management that was chosen or rhythm status at time of discharge. It is interesting to note that the articles in the general management group demonstrated a similar rate of short-term adverse events to the articles in the DCCV and chemical cardioversion groups, many of which required patients to convert to NSR in order to be discharged[15,17-18,20,25-30]. While conversion to NSR seems desirable, particularly in patients with acute onset of AF/AFL, there is no particular reason that persistence of AF/AFL should preclude ED discharge, provided that rate control is adequate and the patient is otherwise stable and not severely symptomatic. This is supported by the articles that observed reasonably high rates of spontaneous conversion to NSR, as well as the studies mentioned that observed high rates of safe discharges, regardless of ED intervention[31,37,38]. Future studies exploring optimal ED management for symptomatic AF/AFL with rate control or observation alone could help elucidate if and when aggressive rhythm control is actually merited.

Limitations

There are several limitations to consider in this review. We performed a qualitative assessment of a somewhat heterogeneous group of articles based on our study design, and thus did not perform any summative statistical calculations for either population baseline characteristics or outcomes. We did not restrict study inclusion based on individual study quality, which may inherently allow for bias in our overall assessment based on the individual study results. Although many of the studies had relatively large sample sizes, some of the studies involved small patient populations, which could limit the external validity of their results[16,21,25,16,21]. Finally, we excluded non-English language studies, and it is possible that in doing so excluded some studies that may have been pertinent to our review.

Disclosures

Dr. Gehi reports grant support from Bristol-Myers-Squib Foundation and speaker's honoraria from Zoll, Biotronik, and Abbott.

Conclusion

This systematic review is the first study to our knowledge to evaluate the optimal management of symptomatic AF/AFL in the ED with a direct impact on ED disposition. Based on our findings, there are several viable strategies to employ, all of which may result in a safe ED discharge to home in the right patient population. A suggested general protocol is included in [Figure 2]. The decision aids included in our study can be helpful for determining which patients can be safely managed in the outpatient setting and which require inpatient evaluation. The use of cardioversion in the ED can help expedite discharge, and DCCV has a higher success rate than chemical cardioversion, but conversion to NSR is not a requisite for a safe ED discharge.Early outpatient follow-up is crucial to prevent repeat ED visits and ensure long-term care.However, future studies of acute AF/AFL care are needed to develop management strategies that are comprehensive, in order to determine best practices and demonstrate scalability of systems of care to a variety of settings.

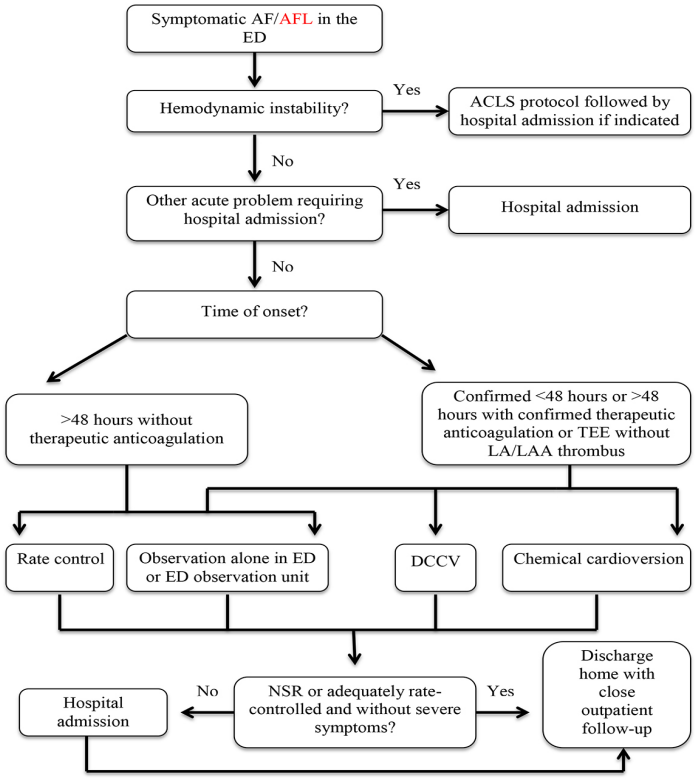

Figure 2: Suggested Protocol for ED Management of AF/AFL

ACLS = advanced cardiovascular life support, AF = atrial fibrillation, AFL = atrial flutter, DCCV = direct current cardioversion, ED = emergency department, LA/LAA = left atrium/left atrial appendage, NSR = normal sinus rhythm, TEE = transesophageal echocardiogram

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LARIAT Trial Updates

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Abstract

The thrombus formed within the LAA is responsible for the vast (about 90%) majority of strokes. Anticoagulation, although effective therapy for stroke prevention is not feasible in a significant minority of patients due to various reasons. Two percutaenous LAA exclusion techniques have been developed in an effort to decrease risk for stroke: endocardial closure/plugging of the LAA (Watchman, Amplatzer devices) and epicardial LAA ligation (LARIAT). The aim of this study is to review the trial data to date for the LARIAT device.

The LARIAT suture has been used in more than 4500 patients with high success of LAA complete closure (92-100%), mostly in the patients unable to take anticoagulation and in a small minority as antiarrhythmic option. The LARIAT technique has evolved with a change in pericardial access method that resulted in dramatic improvement of safety. LAA closure performance with LARIAT system seems to be similar to Watchman device, with small leaks during follow-up in 6-24% of the cases, which do not to correlate with thrombo-embolic events. LAA has been proven to play an important triggering role in patients with persistent atrial fibrillation. Small studies had shown that LAA ligation with LARIAT could terminate persistent atrial fibrillation and possible improve ablation success. Ongoing aMAZE randomized trial is studying if LAA ligaiton using LARIAT suture leads to improved atrial fibrillation ablation success.

Available data suggests that LAA closure using LARIAT epicardial suture is a good alternative for stroke risk reduction in patients who are unable to be on anticoagulation therapy. LARIAT system might improve success of AF ablation for patients with persistent and long persistent AF, pending the results of the ongoing a MAZE trial.

Introduction

The left atrial appendage (LAA) has been considered "the most fatal attachment" of the human body. In patients with non-valvular atrial fibrillation (AF) it is well accepted, based on surgical and transesophageal echocardiography (TEE) studies, that thrombus formed within the LAA is responsible for the vast (about 90%) majority of strokes[1]. The LAA anatomy, with different morphologies, presence of pectineate muscles, and blood flow characteristics predispose to blood stasis and thrombus formation in patients with AF[2,3]. Anticoagulation is the mainstay therapy, and has been proven in multiple randomized trials to be very effective for prevention and treatment of LAA thrombus and to decrease the incidence of stroke. However, this approach is not feasible in a significant minority of patients because they are either non-compliant with medications, are at elevated risk of bleeding, or have already experienced significant bleeding[4].

Surgical closure of the LAA as a standalone procedure or concomitant with cardiac surgery has historically been the only option for closure of the appendage. However surgical closure has a suboptimal success (persistence of flow in LAA reported to be persistent in 30-60%); incomplete closure has been shown to be associated with subsequent thrombo-embolic events[5]. Therefore, a lot of interest has developed in two percutaenous LAA exclusion techniques: endocardial closure/plugging of the LAA (Watchman, Amplatzer devices) and epicardial LAA ligation (LARIAT). The aim of this study is to review the trial data to date for the LARIAT device.

Key Words
Lariat, Appendage Ligation, LAA Ligation

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The LARIAT (SentreHeart, Redwood City, CA) was granted 510k class II clearance by the United States Federal Drug Administration (US FDA) in June 2006 for soft tissue approximation. The system has been used to percutaneously ligate the LAA. It requires guidewires with earth magnets at their tip placed epicardially and endocardially into the LAA following transseptal puncture to facilitate delivery of a suture that snares the LAA epicardially at its ostium. The system has been used as a stroke prevention as well as an antiarrhythmic strategy.

Feasibility of LAA closure using LARIAT suture

The initial canine experience demonstrated complete LAA exclusion in all cases, with progressive LAA atrophy and endothelialization of the LAA orifice[6]. This technique arose to fill an unmet need for reduction of risk for stroke in patients unable to take long term anticoagulation.

The first in human feasibility LARIAT system study was reported by Bartus et al in 2011. Thirteen patients were enrolled; 2 patients receiving the LARIAT during cardiac surgery, 10 patients underwent successful percutaneous ligation of the LAA, and in one patient the suture could not be delivered successfully[7]. The first clinical study was reported by the same investigators from Poland. They were able to successfully deploy the device in 85 (96%) of 89 patients who were unable to take anticoagulation. One patient developed a pericardial effusion during transseptal puncture and 2

had pericardial access complications (one effusion secondary to RV puncture and one superficial epigastric artery laceration requiring cauterization). During follow-up, there were 2 unexplained sudden cardiac deaths and 2 strokes; the latter were felt to be non-embolic. At 3 months and 1 year, 95% and 98% of patients respectively had complete LAA closure confirmed by TEE[8]. This study showed that LARIAT system is a viable option for stroke prevention in patients with contraindication to anticoagulation, with high success rate and acceptable risk for complications.

Success and safety of Lariat procedure

Since these initial studies, the LARIAT has been used in more than 4500 patients in the United States alone[9], mostly in patients with a contraindication to oral anticoagulation. In the process, multiple additional studies have emerged that report on the safety and efficacy of this procedure.

The investigators from the U.S. Transcatheter LAA Ligation Consortium[10] reported the results with LARIAT LAA ligation in 154 patients with a median of CHADS2 score of 3, who underwent a Lariat procedure at one of at 8 US centers. The overall procedural success was 86%; in 9 patients the suture could not be delivered due to either pericardial adhesions, challenging anatomy or need for emergent surgery due to right ventricular perforation. Among the 145 cases in which the suture was delivered, complete LAA closure was accomplished in 133 patients (92%). In the remaining 11 (7%) patients, although there was a residual leak, it was <5 mm in all patients. However, 15 (10%) patients experienced at least one major periprocedural complication; these included major bleeding (n=14, 9%), need for emergent cardiac surgery [n=3 (2%) - 2 for right ventricular perforation and one for LAA perforation], and an in-hospital death (n=1, 0.7%) 19 days after the procedure. During TEE follow-up, a leak < 5 mm was found in 14% of patients and >5 mm in 6% of patients. Finally, a thrombus was identified in 4 (6%) patients, all successfully treated with anticoagulation wihout any sequelae.

Another multicenter series by Miller and colleagues[11] reported 41 patients with a mean $CHADS_2$ score of 3 who underwent a Lariat procedure. Acute LAA closure was achieved in 38 (93%) patients; however, the procedure was complicated by LAA perforation in 4 (9%) patients, 2 of whom required urgent open surgical repair. Pericardial effusions requiring pericardiocentesis occurred in 8 (20%) patients. They also reported early pericarditis in 7 patients and late pericarditis in 5 patients; 2 of the patients with late pericarditis required percutaneous drainage for signs and symptoms of pericardial tamponade. A TEE or CT angio performed ~ 3 months post-procedure showed a residual leak > 1mm in 24% of patients; however, in all patients, the residual leak was < 5 mm. In this series, only one patient had a possible embolic complication, which manifest as amaurosis fugax.

In another multicenter international series, Sievert et al[12] reported a 99% acute closure with the Lariat system in 139 patients with a mean CHADS2 score of 2.4 who were ineligible for anticoagulation. Significant periprocedural complications occurred in 11.5%, which included 2 cardiac perforations and 1 death due to pulmonary embolism. Follow-up TEE, performed at least 1 month post-procedure, showed complete closure of LAA in 90% of patients; in the remaining, a 2-4 mm leak was observed. During a mean follow-up of 2.9 ± 1.1 years, stroke or systemic embolism was observed at a rate of 1% per year (n=4).

The results of these studies and an internal review of the MAUDE database resulted in the issuance of a safety communication by the US FDA on July 13, 2015. They described 45 adverse events reported in the database. Of concern, emergent cardiac surgery was needed in 75% of these patients with an adverse event and 6 patients died. In this communication, the FDA also reminded patients and providers that the safety and effectiveness of the Lariat procedure has not been fully established[13]. However, one of the major limitations of using the MAUDE database in drawing any form conclusions is the lack of a denominator; specifically, there is no way to know how many patients underwent the procedure during this period.

As is common with any new procedure or technique in any field, hurdles are overcome with increased experience, which impoves success and decreases complications. A high peri-procedural rate of complications observed in the initial experience with the Lariat procedure was primarily driven by inappropriate case selection, challenges obtaing epicardial access and uncertainties regarding optimal peri-procedural management. By learning through the initial experinces and making necessary modifications in technique and patient management, a dramatic improvement in safety has been observed,

Lakkireddy et al[14] reported in 2016 on a cohort of 712 patients, the largest study to date, who underwent a LARIAT LAA ligation procedure at one of 18 US centers. This study confirmed the significant improvement in procedural safety that has been observed with increased expertise. For example, a decrease in pericardial access complications occurred when a micropuncture needle replaced a large bore needle for pericardial access [Figure 1][14,15]. The use of colchicine, started prior to the procedure and continued for some time after the procedure, decreased the incidence of delayed pericarditis as well as pericardial and pleural effusions from 8.4% to 1.58%. The use of anti-inflammatory regimens is supported by the anatomic and histologic findings showing a significant inflammatory response in the LAA

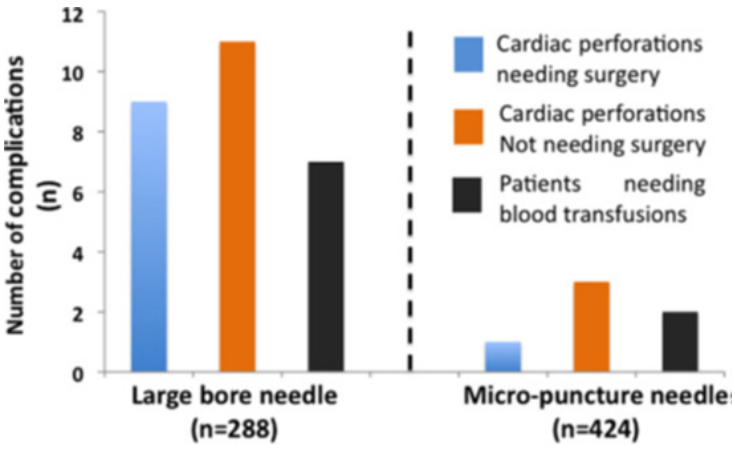

Figure 1: Difference in access site complications after the introduction of a micropuncture needle for pericardial access (Reproduced with permission from Heart Rhythm, Vol 13, No 5, May 2016)

Table 1: Acute procedural complications and the difference between the large bore (LB) Pajunk needle and the micropuncture (MP) needle during LARIAT deployment (Reproduced with permission from Heart Rhythm, Vol 13, No 5, May 2016)

Procedure variable	Total (N=712)	LB needle (n=288)	MP needle (n=424)	P
Procedure-related mortality	1	0	1	NA
Patientes needing open heart surgery	10	9	1	.002
Cardiac perforations without the need for cardiac surgery	14	11	3	.004
Patients needing transfusion	9	7	2	.02
Stroke in the periprocedural period	0	0	0	NA
Injury to superior epigastric, coronary, or internal mammary artery	4	2	2	.7
Total	38	29	9	.0001

Values are presented as counts unless otherwise indicated NA= not applicable

and the left atrium post ligation, that can possible trigger Dressler's syndrome[16]. The overall rate of acute complications decreased from 10.14% to 2.2% (p <1 0.0001, [Table 1]). The acute success of the Lariat procedure was > 95%, with a procedural mortality of only 0.14%.

Mid and long term efficacy of Lariat

Recent data have soght to compare the Lariat to a Watchman LAA closure device (Boston Scientific, Marlborough, MA) which is approved by the US FDA for as an alternative to warfarin for stroke prevention in atrial fibrillation patients at high-risk for stroke. Pillarisetti et al reported on 219 patients treated with a Watchman device and 259 patients treated with a LARIAT device[17]. Patients treated with a Watchman device were older, more likely to be male, had a lower mean CHADS2 score, were less likely to have had prior stroke or heart failure than patients treated with a Lariat device; in contrast, the Lariat patients had a larger left atrium and LAA. There were no deaths periprocedurally in either group. Significant complications included groin hematoma (n=1), pericardial effusion requiring drainage (n=2), and device embolization (n=1) in the Watchman group and cardiac tamponade requiring urgent surgical repair (n=4) in the Lariat group. Of note, all cardiac tamponades occurred in the early experience; none ocurred after switching to a micropuncture needle for pericardial access.

Post procedure, all Watchman patients received anticoagulation for at least the first 6 weeks followed by clopidogrel out to 6 months; in contrast, 30% of patients in the Lariat group received only antiplatelet drugs and only 31% of patients in Lariat group were treated with anticoagulation. Follow-up TEE at 30-90 days and 9-12 months showed that the Watchman group had a higher incidence and size of peri-device leak (21% vs 13% p = 0.019; 3.1 ± 1.1 mm vs. 2.15 ± 1.4 mm, respectively, [Figure 2]). This did not translate into differences in incidence of thrombus identification or TIA/stroke events between the groups [Table 2]. Furthermore, the neurologic events occurred in patients not on anticoagulation and did not correlate with presence of leaks or thrombus. This finding was debated in another series of 98 patients reported by Gianni et al.[18]. They report acute LAA closure in 95% of the patients with 20% leaks seen in follow-up on 3D TEE at one year (some of the leaks would have been missed on 2D TEE). There were 5 patients, all off anticoagulation, who suffered a TIA or stroke. In the 3 patients in whom TEE information was available, all had a small (<5 mm) leak; however no thrombus could be identified. Their conclusion was that incomplete occlusion of the LAA after LARIAT ligation is common [Table 3&4] and may be associated with thromboembolic events.

Table 2: Differences in the incidence of thrombus or transient ischemic attack (TIA)/stroke in patients with and without leaks in the Watchman and Lariat groups (Reproduced with permission from Pillarisetti et al., Heart Rhythm, Vol 12, No 7, July 2015)

	Watchman group (N=219)		Lariat group (N=259)	
If leak or not	Leak (n=46)	No Leak (n=173)	Leak (n=33)	No Leak n=(222)
Thrombus (n)	2	6	2	2
TIA/stroke (n)	1 (thrombus)	2	1 (no thrombus)	2
Noncerebral embolism	0	0	0	0

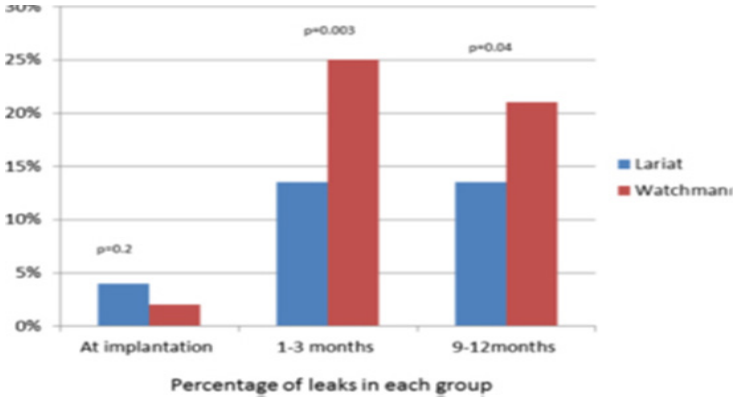

Figure 2: Comparison of prevalence of leaks in both groups at different follow-up times (Reproduced with permission from Pillarisetti et al., Heart Rhythm, Vol 12, No 7, July 2015)

In the LAA-LA AF registry an incomplete LAA ligation was found in 11 (12%) of the patients (1-3 mm in 7 patients and 4-5 mm in 4 patients) that occured in all LAA morphologies. Despite incomplete ligation, mean LAA size and volume, as measured by CT angio pre and one month post ligation, were significantly smaller beyond ligation, by 66% and 67% respectively, suggestive of LAA remodeling[19]. The remodeling of the LAA post ligation has been nicely demonstrated anatomically and histologically by Bartus K et al in 2 cases in whom the heart was explanted (one at autopsy and one after transplant) showing that LARIAT LAA ligation resulted in extensive LAA inflammation leading to fibrosis and scarring[16].

Table 3: Reported incidence of overall leaks rate after LAA ligation with the Lariat Device (Reproduced with permission from Gianni et al., JACC Interv, Vol 9, No 10, May 2016)

First Author (Year) (Ref.#)	n*	Follow-Up Imaging	Acute	Early (<6 months)	Late (6-12 months)
Bartus et al. (2013) (13)	85, 81, 65	2D TEE	4%	5%	2%
Massumi et al. (2013) (13)	20, 17, 17	2D TEE	0%	6%	6%
Stone et al. (2013) (13)	25, 22	2D TEE	0%	0%	NA
Miller et al. (2014) (25)	41, 41	2D TEE, CT	7%	24%	NA
Price et al. (2014) (26)	145, 63	2D TEE	8%	20%	NA
Pillarisetti et al.(2015) (27)	259, 259, 259	2D TEE	2%	13%	13%
This Study	98,96, 96	2D TEE, 3D TEE	5%	15%	20%

*Number of patients with fallow-up TEE across the 3 time points 2D=2-Dimentional; 3D=3-Diamentional; CT=Computer tomography; NA=not available; TEE=transesophageal echocardiography

Other potential applications of LARIAT suture

More recently it had been recognized the arrhythmogenic role of LAA in patients with AF, especially in those with persistent and long persistent AF. In a series of 987 patients, 71% non-paroxysmal AF, DiBiase et al.[20] reported impulses firing from LAA in 27% of the patients at re-do procedures. Interestingly enough, in 8.7% of the patients the LAA was the only source of arrhythmia with no pulmonary vein reconnection or other extra-pulmonary vein site triggers. Ablation and electrical isolation of the LAA showed significant decrease of AF recurrence in follow-up. This led to BELIEF trial[21] in which patients were randomized to undergo electrical LAA isolation in addition to extensive ablation vs. extensive ablation. Isolation of the LAA led to significantly increased percentage of recurrence free patients after single procedure (56% vs. 28%), and isolating the appendage in both groups at redo procedure resulted in a cumulative success in 76% vs. 56% at 24 months after an average of 1.3 procedures. However due to decrease LAA motility after electrical isolation there was an increased risk of thrombus formation and patients needed to be maintained long term on anticoagulation. With this knowledge LARIAT suture was seen as a possible therapeutic solution that could achieve both electrical isolation and stroke prevention. Closure of the LAA with LARIAT had shown acute decrease or complete elimination of LAA voltage[22]. Badhwar et al[23] reported in a series of 162 patients with persistent or long persistent AF who underwent Lariat LAA ligation that 13 patients (8%) spontaneously converted to sinus rhythm acutely or within 1-2 days and maintained sinus rhythm during a follow-up period of 15.8 ± 10.5 months (range 1-36 months), suggesting again the importance of LAA in triggering and maintaining AF. The impact of adding LARIAT closure of LAA to a conventional AF ablation procedure in patients with persistent AF was reported in a prospective observational series reported by Lakkireddy et al in LAALA-AF Registry[24].

The LARIAT cohort included 69 patients who underwent first LAA ligation using LARIAT suture followed by a conventional AF ablation procedure, mainly pulmonary vein isolation, at least 30 days afterwards. The results were compared to a sex and age matched cohort who underwent conventional ablation only during the same time frame. Freedom from atrial fibrillation or tachycardia at 12 months off antiarrhythmic therapy after 1 ablation procedure was 65% in the LARIAT group compared to 39% in the conventional group (p = 0.002) [Figure 3]. At the time of the AF ablation the LAA was electrically silent in all the patients with complete LAA ligation and in 73% of patients with incomplete LAA ligation. The patients with electrically active LAA underwent LAA isolation. Maintenance of sinus rhythm without antiarrhythmic drugs was similar in the group with leaks when compared with the group without leaks (64% vs 73%, p = 0.6)19.

Besides electrical isolation with elimination of the possible LAA triggers, there are other outcomes, unique to LAA ligation, that likely are contributing to success of AF management as revealed by DJ Lakkireddy et al in "The LAA HOMEOSTASIS STUDY"[25]. In this study blood concentrations of multiple hormones implicated in adrenergic, renin-angiotensin-aldosterone and metabolic systems, as well as natriuresis were evaluated immediately before the procedure

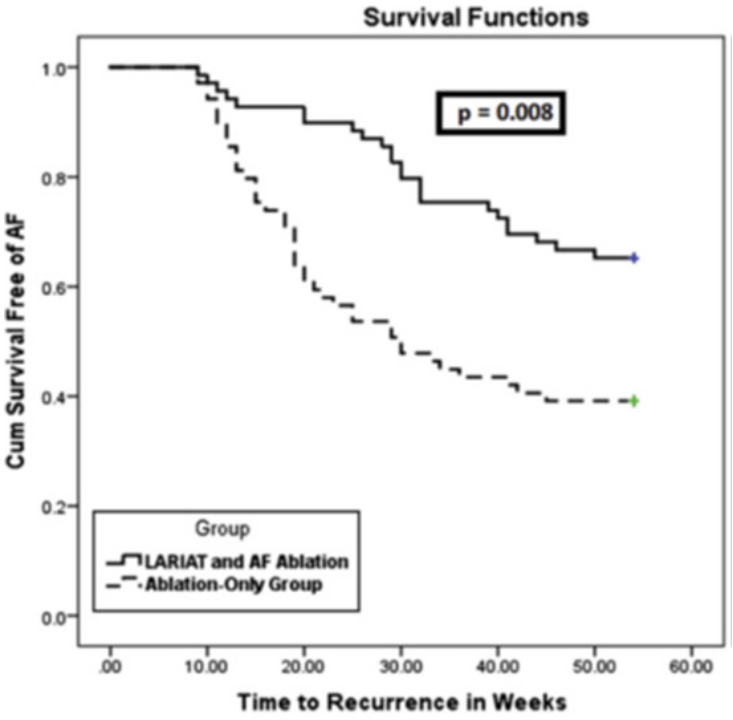

Figure 3: Survival analysis using Kaplan-Meier curve of the primary outcome in both groups (Reproduced with permission from Lakkireddy et al., JACC Clinical EP, Vol 1, No 3, 2015)

and after device deployment, at 24 h, and 3 months follow-up in 38 patients who underwent epicardial LAA ligation and 39 patients who underwent endocardial LAA occlusion. When compared with endocardial LAA closure the adrenaline, noradrenaline, aldosterone and renin were significantly lower at 24 h and 3 months. This was also associated with sustained lower blood pressure at 3 months in the epicardial ligation group (median [interquartile range] SBP 138.60 [20.10] to 117.90 [12.80] and DBP 81.90 [14.90] to 70.90 [14.95], p < 0.01 respectively), compared with no significant difference in the endocardial closure group 25. However the atrial and brain natriuretic peptide levels after initial variations were unchanged at 3 months, replicating the findings of Bartus et al in a study of 66 patients undergoing LARIAT LAA ligation[26].

Another potential benefit of LAA ligation has been shown by Badhwar et al.[27] in a small study of 22 patients which demonstrated the feasibility and safety of staged LAA ligation and pulmonary vein isolation for treatment of atrial fibrillation. In a subgroup of 10 patients whom were in sinus rhythm prior to LAA ligation there was a significant reduction of p wave duration and dispersion after LARIAT LAA ligation that persisted after pulmonary vein isolation (from 106 ± 16 msec to 97 ± 19 msec following LAA ligation and remained reduced (95 ± 12 msec following PVI). This likely demonstrates electrical remodeling, previously showing to be a predictor of ablation success[28].

These results made the basis for the ongoing aMAZE prospective trial in which the patients with persistent and long persistent AF are randomized to either LARIAT LAA ligation followed at least 30 days after by pulmonary vein isolation and cavo-tricuspid isthmus ablation or to pulmonary vein isolation and cavo-tricuspid isthmus

Table 4: Reported incidence of overall leaks rate after LAA ligation with the Lariat Device (Reproduced with permission from Gianni et al., JACC Interv, Vol 9, No 10, May 2016)

Stroke Prevention Studies	N	Procedural success	Complete occlusion < 1mm leak	Leak < 5mm	Peri-procedural complications					
					Total	Device related	Death	Cardiac tamponade	Emergent surgery	Pericardial effusion w/o intervention
Bartus K 2011	13	12/13(92%)	12/12 (100%)	0	1(8%)	1	0	0	0	0
Bartus K 2013	89	85/89(96%)	82/85(96%)	3(4%)	3(3.4%)	0	0	2	0	0
Massumi A 2013	21	20/20(100%)	19/20(95%)	1 (5%)	2(10%)	0	0	2	1	0
Price MJ 2014	154	145/154(94%)	133/145(92%)	11 (7%)	15(9.7%)	5	1	7	3	16
Miller M 2014	41	38/41(93%)	38/38(100%)	0	20/41(49%)	4	0	8	2	7
Lakkireddy DJ 2016	712	682/712(95.5%)	669/682(98%)	13(2%)	29/288(10.1%)	NR	0	11	9	0
Bartus K 2011	13	12/13(92%)	12/12 (100%)	0	1(8%)	1	0	0	0	0
					9/424(2.1%)	NR	1	3	1	0
Bartus K 2016	58	58/58(100%)	58/58(100%)	0	0	0	0	0	0	0
AF Reduction Studies										
Lakkireddy DJ2014	69	69/69(100%)	69/69(100%)	0	3/69(4%)	0	0	1	0	0
Afzal MR 2015	50	50/50(100%)	50/50(100%)	0	6/50(12%)	0	0	0	0	4

ablation alone[29]. The trial had finished the enrolment for the initial early stage of 175 patients and interim analysis by DSMC and FDA did not suggest any safety concerns or performance issues, allowing proceeding to the 2nd stage up to 600 patients. The results should be available in the next few years.

New and future developments

Currently the second generation of LARIAT system is available, LARIAT +, system that was developed from the experience and lessons learned with the initial system. The new system has a larger snare accommodating LAA diameters up to 45 mm and has now a steel braided shaft that provides increased columnar strength within the shaft allowing better torque-ability to overcome any influence of the epicardial sheath, and a platinum-iridium "L" marker has been placed in the distal tip of the LARIAT for easy detection of correct orientation under fluoroscopy. Initial experience with this new system has been reported by Bartus et al in 58 patients[30]. The acute success was high, all the patients having complete acute closure. There were no device or procedural related complications, only one late pericardial effusion at 30 days that required pericardiocentesis. In follow-up at 1 month and 3 months, TEE showed 96.3% and 92.3% LAA closure respectively, with no leaks greater than 3 mm. There were no strokes, embolic events or deaths after 12 months.

Future improvements of the system are either in evaluation or in conceptual phases including cutting of the snare prior to removal from the base of LAA and possible direct visualization of the ligation process.

Conclusion

LARIAT suture provides high success of LAA closure with long term results comparable to FDA approved Watchman device. Available data suggests that LAA closure using LARIAT epicardial suture is a good alternative for stroke risk reduction in patients who are unable to be on anticoagulation therapy. With experience and technique change safety of the procedure improved dramatically. LARIAT system might improve success of AF ablation for patients with persistent and long persistent AF, pending the results of the ongoing aMAZE trial.

Conflict of interest

None.

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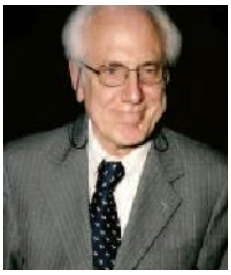

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