JAFIB
Original Research
Journal of Atrial Fibrillation
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IntravenousCorticosteroid Use Is Associated With Reduced Early Recurrence of Atrial Fibrillation Immediately Following Radiofrequency Catheter Ablation

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Abstract

Background

Early recurrence of atrial fibrillation (ERAF) occurs in up to 40% of patients after radiofrequency catheter ablation for atrial fibrillation (RFCA), increasing hospital stay, need for anti-arrhythmic medications (AADs) and cardioversion, and, possibly, the risk of future AF. It has been postulated that inflammation plays a key role in developing ERAF. Short term postoperative use of corticosteroids to reduce ERAF post-RFCA has not been vigorously studied.

Methods

This was a case-control study of consecutive patients undergoing RFCA for the management of AF at a single-institution. RFCA was performed by a single operator from October 2005 through July 2009. Patients receiving intravenous corticosteroids immediately following the ablation and for 48 hours (6 doses) constituted the treatment group. Controls received no intravenous corticosteroids during their hospitalization. All other management strategies were similar between the 2 groups, including the administration of AADs post- operatively. All patients had continuous electrocardiographic monitoring throughout their hospitalization. Multivariable logistic regression analysis was used to determine the impact of intravenous corticosteroids on ERAF defined as any AF>10 minutes during hospitalization.

Results

A total of 68 patients undergoing RFCA for the management of AF were included in this analysis. The overall ERAF rate, irrespective of intravenous corticosteroid use, was 23.5%. The administration of intravenous corticosteroids (n=37; mean±SD dexamethasone mean dose 11.9±4.6 mg/day; range 4-16 mg/day) was associated with an 82% reduction in patients' odds of ERAF (adjusted odds ratio; 0.18, 95% confidence interval [CI] 0.04 to 0.78) compared with those who did not receive corticosteroids (n=31). A dose-response effect was also observed, with a 17% reduction in ERAF odds for each dexamethasone mg-equivalent administered (adjusted odds ratio; 0.83, 95%CI 0.73 to 0.96).

Conclusions

The use of intravenous corticosteroids was associated with a dose-dependent reduction in the odds of developing ERAF after RFCA for the management of AF.

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Introduction

Radiofrequency catheter ablation (RFCA) for symptomatic patients with atrial fibrillation (AF) not responding to conventional pharmacological management has become an effective treatment strategy in many centers. [1,2] Early recurrence of atrial fibrillation (ERAF) has been found to occur in up to 40% of patients following RFCA for the management of AF. Some investigators have found a 2-3 fold increased risk for future AF development .[3-5]At our center ERAF is responsible for more intensive care, including additional medications and cardioversion for many inpatients. ERAF also constitutes a significant source of consternation and stress for many patients.

Corticosteroids are potent anti-inflammatory agents that affect numerous components of the inflammatory response. [6] Studies have indicated that the release of pro-inflammatory markers such as C-reactive protein (CRP), white blood cells (WBCs), interleukin (IL)-6 and 8 and tumor necrosis factor (TNF)-alpha may play a significant role in the initiation, maintenance and perpetua tion of various types of AF, [6-7] including ERAF following RFCA for AF. [3-5, 8-11] Corticosteroids have also been shown to reduce the development of post-cardiac surgery AF. [12] The present study sought to determine the association between short-term, immediate post-RFCA intravenous corticosteroid use and the development of ERAF.

Methods

This was a retrospective case-control evaluation of a cohort of consecutive patients who underwent RFCA at a single institution by a single operator between October 2005 and July 2009. All patients underwent RFCA for paroxysmal or persistent AF per the institution's standard protocol. Data was gathered from the medical, pharmacy and billing records of all eligible patients.

The primary aim of this evaluation was to determine whether intravenous corticosteroids (at any dose) reduce ERAF following successful RFCA. ERAF was defined as occurrence of AF lasting at least 10 minutes (as documented by a rhythm strip or ECG) any time prior to hospital discharge. Length-of-stay (LOS) and safety endpoints were also evaluated.

Preablation Management:

All patients had a multi-slice CT or MRA performed within 1 month of admission for a 3D reconstruction of the left atrium and pulmonary veins. Patients who had paroxysmal atrial fibrillation had an electrocardiogram within 48 hours of their admission to be sure that they were in normal rhythm and that warfarin could be discontinued without performing transesophageal echocardiography (TEE) or cardioversion. For patients in persistent atrial fibrillation, an outpatient or inpatient TEE was done within 48 hours of their planned admission for ablation. They were bridged from warfarin to procedure with subcutaneous enoxaparin or dalteparin therapy. If a clot was detected, atrial fibrillation ablation was deferred. Anti-arrhythmic drug therapy was discontinued for 5 half lives prior to admission. Amiodarone was discontinued for 2 weeks preoperatively. All patients had an admission electrocardiogram (ECG) and were consented for the procedure.

Ablation Procedure:

All patients were under the care of an anesthesiologist. All had a 4-French arterial blood pressure monitoring line placed in the right femoral or left femoral artery. Sheaths and catheters were placed through both femoral veins, and occasionally through the right internal jugular vein. Left atrial/pulmonary vein access was achieved through a trans-septal puncture using the Brockenbrough technique. Anticoagulation with intravenous heparin was started to achieve an ACT 350-400 sec.

Electroanatomic mapping with the ESI - NAVX contact mapping system (St. Jude Medical, St. Paul, MN) was employed for all patients. Images from the preoperative 3D CT or MRA were fused with the 3D electroanatomic map when possible. A Boston Scientific 5 mm tipped, extended large-curve (Boston Scientific, Natick, MA) or Daig large curve 5 mm tipped (St. Jude Medical, St. Paul,. MN) radiofrequency catheter was used in all patients to isolate the pulmonary veins, and create linear roof and mitral valve lesion sets, when appropriate. Radiofrequency was temperature controlled at

50-60 degrees centigrade with a maximum energy up to 50 watts. Each lesion was delivered for 10-20 seconds at ≥50 degrees and then moved to an adjacent site. An esophageal temperature probe was used to monitor esophageal lumen temperatures.

All patients undergoing ablation for paroxysmal AF underwent a full electrophysiologic evaluation with pacing from the right ventricular septum and both right and left atria. Identification of triggering arrhythmias, concomitant flutter, and characterization of right and left atrial vulnerability was considered important information. In the paroxysmal atrial fibrillation patient in nor-

Table 1 Patient Characteristics

Variable	**ERAF (N=16) n (%)**	**No ERAF (N=52) n (%)**	P-value*
Peri-Operative Corticosteroid Use	5 (31.3)	32 (61.5)	0.03
Dexamethasone	4 (25.0)	32 (61.5)	0.02
Hydrocorticosone	1 (6.3)	0 (0)	0.24
Daily Dose of Peri-Operative Corticosteroids (mean±SD in dexamethasone equivalents, milligrams)	2.23±3.85	7.77±7.06	<0.01
Age >50 years	13 (81.3)	33 (63.5)	0.23
Age (mean±SD, years)	62.13±10.66	53.21±9.13	0.02
Male Gender	13 (81.3)	38 (73.1)	0.74
Paroxysmal Atrial Fibrillation	11 (68.8)	27 (51.9)	0.24
Prior Myocardial Infarction	2 (12.5)	4 (7.7)	0.62
Prior Cerebrovascular Disease	2 (12.5)	3 (5.8)	0.58
LVEF (mean±SD)	55.67±8.63	55.19±9.18	0.86
Heart Failure	0 (0)	8 (15.4)	0.18
Diabetes Mellitus	3 (18.8)	5 (9.6)	0.38
Hypertension	8 (53.3)	29 (55.8)	0.87
Chronic Obstructive Pulmonary Disease	2 (12.5)	1 (1.9)	0.14
History of Tobacco Use	2 (13.3)	10 (19.2)	0.72
Mitral Regurgitation	2 (13.3)	6 (11.5)	>0.99
Medication Use:			
Beta-Blockers	9 (56.3)	29 (55.8)	0.93
ACE inhibitors or ARBs	6 (40.0)	18 (36.0)	0.78
Calcium Channel Blockers	3 (20.0)	16 (32.0)	0.52
Statins	8 (53.3)	18 (36.0)	0.23
Digoxin	4 (25.0)	3 (5.8)	0.05
Anti-Arrhythmics	7 (43.8)	35 (67.3)	0.09
Anticoagulants	15 (93.8)	41 (78.8)	0.27

ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; ERAF=early recurrence of atrial fibrillation; LVEF=left ventricular ejection fraction; SD=standard deviation; TIA=transient ischemic attack
*All variables with a p-value <0.2 were included in the multivariable logistic regression model

mal rhythm, identification of left atrial, and pulmonary vein potentials in pulmonary veins was performed using either circular (Lasso, Spiral)or standard multi-polar catheters (entrance).

Pacing was performed from inside the ostia of all pulmonary veins to document exit of electrical activity to the left atrium (exit). These areas were tagged using the NAVX system for localization. Pulmonary vein isolation was performed by encircling the pulmonary veins and documenting absence of pulmonary vein signals within each vein (entrance block), and absence of left atrium stimulation while pacing from within the veins at 5 mA (exit block) from the same multiple pacing sites marked prior to the ablation. Roof lines and mitral valve lines were not typically performed Patients in persistent atrial fibrillation did not have a pre-ablation electrophysiologic study.

Baseline intervals including AF mean cycle length (10 beats), H-V interval, presence or absence of delta activity, and QT intervals were recorded. The left atrium including all pulmonary veins, appendage, and mitral annular area were carefully mapped with multi-polar (10-20 poles) catheters. Catheters were left in place in regions around the pulmonary vein ganglionic sites and around areas known to be frequent rotor or driver sites (pulmonary vein ostia, posterior septum) for 5-10 seconds. In each case, areas where there was consistent continuous fractionated electrogram were so marked as "rotors or drivers." The complete ablation procedure involved pulmonary vein isolation and was performed anatomically using a wide circumferential isolation procedure, a roof and anterior mitral valve line (eradication of electrograms >0.5 mV at the radiofrequency application sites were considered endpoint for each burn; bidirectional block was not confirmed). CFEs which were stable (rotors) were marked and ablated (eradicated).

Table 2 Independent Predictors of ERAF Identified in the Multivariable Model

Variable	P-value	AOR	95%CI
Peri-Operative Corticosteroid Use	0.02	0.18	0.04-0.78
Mean Dose of Corticosteroid (per mg)	0.01	0.83	0.73-0.96
Age (per year)	0.01	1.13	1.04-1.23
Digoxin Use	0.04	7.84	1.16-53.1

AOR=adjusted odds ratio; CI=confidence interval; mg=milligram

In patients who converted from atrial fibrillation to atrial flutter or an atrial tachycardia which could not be terminated, a cardioversion was performed to restore normal rhythm. The endpoint was termination of AF with entrance and exit block at all pulmonary veins.

There were no changes in the ablation methods or endpoints over the duration of this study.

Post-Ablation Management and Follow-Up:

All patients (both arms) were continuously monitored during their hospitalization and received anti-arrhythmic drugs as well as anti-thrombotic therapy with IV heparin and were transitioned to adjusted dose warfarin. Patients who had recurrent atrial arrhythmias were cardioverted prior to discharge once they were properly loaded with anti-arrhythmic drugs. Patients were discharged in NSR when the INR was >= 2.

Statistical Analysis:

Continuous variables are presented as means with standard deviations and are compared between groups using a Student's t-test or Mann- Whitney test (when appropriate). Dichotomous variable are presented as percentages and compared between groups using chi-squared analysis or Fischer's exact test (where appropriate).

Given the observational study design, important differences in observed demographic and pre-procedure variables were likely to occur which could bias the treatment effect. Therefore, we conducted multivariable logistic regression to control for potential confounders in our evaluation.

We first conducted univariate analysis to examine the association of the endpoint of interest (ERAF as the dependant variable) with several variables in our pre-procedure demographic (independent

variables). All the variables with a p-value of <0.20 in the univariate analysis were entered into the multivariate logistic regression model. In the multivariate model, a p-value of <0.05 was considered significant. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) were calculated for all independent predictors. Statistical analysis was performed with SPSS version 17.0 (SPSS, Chicago, IL, USA).

Results

A total of 68 patients who underwent RFCA for the management of AF were included in our analysis. Patient characteristics are detailed in Table 1. Thirty-seven patients received intravenous corticosteroids and 31 did not. The average dose of corticosteroids in dexamethasone equivalents was 11.9±4.6 mg/day, with a range of 4-16 mg/day. All 68 patients received post-ablation anti-arrhythmic medications (AADs). There was no significant difference in the types of AADs used between the 2 groups.

Overall, ERAF occurred in 16 (23.5%) patients irrespective of intravenous corticosteroid use. Upon multivariable logistic regression analysis (Table 2), the administration of intravenous corticosteroids was associated with an 82% reduction in patients' odds of ERAF compared with those who did not receive corticosteroids. The effect of intravenous corticosteroids on ERAF was not statistically different in those undergoing RFCA for treatment of paroxysmal (AOR 0.14, 95%CI 0.02 to 1.28) or persistent AF (AOR 0.10, 95%CI 0.01 to 1.03, p-value for interaction=0.83). For each milligram of dexamethasone equivalents administered, a 17% reduction in the odds of ERAF occurred. Patient age and digoxin use were also found to be independent positive predictors of ERAF. Anti-arrhythmic drugs use even though a univariate predictor was not found to be a significant independent predictor in reducing ERAF.

Median LOS was 3.0 days in both the intravenous corticosteroid and no corticosteroid groups (p=0.59). Only one patient had an infectious complication (urinary tract infection in the corticosteroid group) during the hospital admission. There were no bleeding episodes. No patient required a change in their glycemic control.

Discussion

RFCA has become an important option in treating patients with symptomatic atrial fibrillation who are not responding to conventional drug therapy .[1] However, despite improvements in technical approach ,[2] ERAF following RFCA remains a concern. ERAF has been found to occur in nearly 40% of patients undergoing RFCA for management of atrial fibrillation ,[3,11,14] often necessitating extended LOS, additional cardioversions, and increased healthcare expenditures.

While this study did not address the affect of ERAF on long term outcomes, a case-control study conducted by Richter et al. showed that recurrence of atrial fibrillation in the first 48 hours post-ablation was a statistically significant predictor of long-term (median follow up of 12.7 months) ablation failure (hazard ratio 2.17, 95%CI 1.45 to 3.25). Richter et al. proposed that reduced atrial fibrillation burden post-RFCA allowed for earlier initiation of reverse remodeling, leading to favorable anatomic, electrical and functional changes in the atrium, which in the end translated into better long-term ablation outcomes. [3]

The precise pathophysiology of atrial fibrillation post-RFCA is not entirely understood. Incomplete pulmonary vein isolation ablation lines, focal areas of rapid firing in the left atrium, and recovery of conduction in previously ablated muscle fascicles all may explain its reoccurrence. [15] There is also evidence that inflammation may be an important cause of ERAF. [4,14] Histopathologic examination of the myocardium after RFCA in the acute phase has demonstrated the presence of coagulation necrosis, interstitial hemorrhage and edema, followed by infiltration of inflammatory cells. [16,17]

Corticosteroids are potent anti-inflammatory agents that affect numerous components of the inflammatory response and therefore may have utility in preventing post-procedural atrial fibrillation. [13] In a study conducted by McCabe et al. evaluating inflammation as a predictor of the post-ablation ERAF, patients with early recurrence were found to be 21-fold more likely to have increased C-reactive protein levels (OR 21, 95%CI 1.1 to 417, p=0.045) .[4]In yet another study, pre-ablation white blood cell count was found to be a multivariate pre-

dictor of atrial fibrillation recurrence in patients undergoing RFCA for atrial fibrillation .[6,9]

Perhaps the most compelling data supporting the antifibrillatory effect of corticosteroids is in area of prevention of post-cardiac surgery atrial fibrillation. A meta-analysis of 9 randomized controlled trials (n=990 participants) conducted by Baker et al. demonstrated that corticosteroids could significantly lower patients' risk of developing post-coronary artery bypass grafting and/or valve surgery atrial fibrillation by 45% (OR 0.55; 95%CI 0.40 to 0.78). [12]

A recent randomized control trial showed that corticosteroids decreased the incidence of both early (7% vs. 31%) and 14 month recurrence (29% vs. 15%) of atrial fibrillation compared to placebo following RFCA. The authors also showed statistically significant decreases in CRP levels and body temperature in the corticosteroid arm supporting the direct anti-inflammatory effect of corticosteroids in the post-RFCA patient. [18] Our study results, although restricted to the recurrence of atrial fibrillation immediately after RFCA are in agreement with this study.

Limitations

This is a single center observational study. We can only say there is an association between intravenous corticosteroid administration and the decrease in post-RFCA ERAF. We cannot prove causality.

Left atrial size, which is shown to be an important determinant of atrial fibrillation, was not available for all the patients. This could have potentially influenced our results. But in the 70% patients that it was available, it was not found to be statistically different.

We did not attempt to answer the question of whether the use of IV corticosteroids post RFCA for AF would reduce long term recurrence of AF. A larger study population would have been needed to adequately assess long term outcomes.

Conclusions

In our study, the use of intravenous corticosteroids was associated with a dose-dependent reduction in the adjusted odds of developing ERAF after RFCA for the management of AF. The group receiving corticosteroids had an independent and significantly reduced incidence of ERAF. Large randomized controlled trials should be conducted in order to confirm these results, assess the safety of corticosteroids in this setting, and to determine optimal administration and dosing.

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