**Retrospective Study**

The Role of ACE Inhibitors and Angiotensin Receptor Blockers in Cryoballoon Ablation Outcomes for Paroxysmal Atrial Fibrillation.

The Role of ACEi and ARB in cryoballoon ablation for paroxysmal Atrial Fibrillation

Ibragim Al-Seykal, Abhishek Bose, Parag A Chevli, Zeba Hashmath, Nitish Sharma, Ajay K Mishra, Douglas Laidlaw
Abstract

BACKGROUND

Cryoballoon ablation (CBA) is recommended for patients with paroxysmal atrial fibrillation (AF) refractory to anti-arrhythmic drugs. However, only 80% of patients benefit from an initial CBA. There is growing evidence that pretreatment with angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) decreases the recurrence of AF post ablation, particularly in non-paroxysmal AF undergoing radiofrequency ablation. The role of ACE-I and ARB in patients with paroxysmal AF in CBA remains unknown. We decided to investigate the role of ACE-I and ARB in preventing the recurrence of atrial arrhythmias (AA) following CBA for paroxysmal AF.

METHODS

We followed 103 patients (Age 60.6 ± 9.1 years, 29% women) with paroxysmal AF undergoing CBA for one-year post procedure. Recurrence was assessed by documented AA on EKG or any form of long-term cardiac rhythm monitoring. A multivariable Cox proportional hazard model was used to assess if ACEi or ARB treatment predicted the risk of AA recurrence.

RESULTS

After a one-year follow-up, 19 (18.4%) participants developed recurrence of AA. Use of ACE-I or ARB therapy was noted in the study population. Patients on ACEi/ARB had a greater prevalence of hypertension and coronary artery disease. On a multivariate model adjusted for baseline demographics and risk factors for AF, ACEi or ARB therapy did not prevent the recurrence of AA following CBA (p=0.72). Similarly, on Kaplan-Meier analysis pretreatment with ACEi / ARB did not predict the time to first recurrence of AA (p = 0.2173).

CONCLUSION

In our study population, pre-ablation treatment with an ACEi or an ARB had no influence on the recurrence of AA following CBA for paroxysmal AF.
Key Words: ACEi; ARB; Paroxysmal Atrial fibrillation; Cryoballoon ablation; outcome

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Core Tip: We investigated the role of ACEi and ARB in preventing the recurrence of atrial arrhythmias following the cryoballoon ablation (CBA) for paroxysmal AF. Outcomes of 103 patients were evaluated in a retrospective chart review. In our study population, pre-ablation treatment with an ACEi or an ARB had no influence on the recurrence of AA following CBA for paroxysmal AF. To our knowledge, this study is the first of its kind which has examined the effect of ACEi/ARB use in this exclusive subset of patients.

INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia that represents an evolving, global epidemic. It is estimated that the number of Americans afflicted by AF will increase from the current 2.3 million to more than 10 million by 2050. Due to a substantial increase in incidence and prevalence of AF over the past few decades, it presents a significant economic burden on the health care system. In 2014, in the United States alone, an estimated 599,790 emergency department (ED) visits, 453,060 hospitalizations, and 21,712 deaths were associated with AF as a primary medical diagnosis. Furthermore, the mean cost per hospitalization for patients with a primary diagnosis of AF was $8,8194.

Even though Cryo-balloon ablation (CBA) therapy is beneficial in patients with paroxysmal AF refractory to anti-arrhythmic drugs, only 80% of patients benefit from an initial CBA. Myocardial fibrosis is a known risk factor for the development of AF and angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers...
(ARB) are known agents that prevent remodeling. There is growing evidence that pretreatment with ACEi and ARB decreases the recurrence of AF post ablation, particularly in non-paroxysmal AF undergoing radiofrequency (RF) ablation. The role of ACEi and ARB in patients with paroxysmal AF in CBA remains unknown. In this study, we aimed to investigate the role of ACEi and ARB in preventing the recurrence of atrial arrhythmias (AA) following CBA for paroxysmal AF.

**MATERIALS AND METHODS**

**Study design and definitions:**

We performed a single-center, retrospective, cross-sectional study in a community-based tertiary care center in Worcester, MA. Paroxysmal AF was defined as non-sustained episodes of AF converting to sinus rhythm in less than seven days. Patients were required to be on an ACEi or ARB for a minimum duration of four weeks. Institutional review board approval was obtained before initiation of the study.

**Inclusion and exclusion criteria:**

To be included in this study, participants had to be 18 or older and have had CBA as a first or repeat procedure for paroxysmal AF, between January 2015 and April 2018. We excluded all patients with a diagnosis of permanent and persistent AF. Following inclusion data on baseline demographics, concomitant comorbidities, clinical, laboratory, echocardiographic, pharmacologic and ablation procedural details and outcome details were obtained by trained physicians from chart review.

**Cryoablation procedure:**

All CBA were conducted under general anesthesia. Two sheaths (7 Fr. and 9 Fr.) were placed in the left femoral vein following ultrasound-guided vascular access. With the
fluoroscopic guidance, an intracardiac echocardiography (ICE) catheter was advanced into the right atrium and a decapolar mapping catheter was positioned within the coronary sinus. A transseptal sheath was placed through the right femoral vein approach. Heparin was administered intravenously for an activated clotting time greater than 300 seconds to prevent intraprocedural thromboembolic events. Transseptal access to the left atrium was obtained under fluoroscopic and ICE guidance. The trans-septal sheath was then exchanged for a 12 Fr. Flexcath sheath (Medtronic, Minneapolis, MN) which was then utilized to advance a 28-mm Arctic Front Advance Cryoballoon ablation catheter (Medtronic, Minneapolis, MN) with the Achieve spiral mapping catheter into the left atrium. An electroanatomic map of the left atrium and all pulmonary veins was performed utilizing 3-dimentional mapping software (Abbott Cardiovascular, Santa Clara CA), guided by a three-dimensional CT recreation of the LA. Each of the pulmonary veins were then isolated using CBA. During the right-sided pulmonary vein ablation, the decapolar catheter was withdrawn to the superior vena cava to pace the diaphragm and allow for monitoring of phrenic nerve injury. For pulmonary veins with incomplete isolation following CBA, local RF ablation was performed as needed to provide complete isolation. All pulmonary veins have demonstrated a bidirectional conduction block and a post-ablation voltage map was created using the mapping software.

Follow up for Ablation success:

The patients with paroxysmal AF undergoing CBA were followed for one-year post procedure for any development of AA. The recurrence of AA was assessed through a medical records review by documented self-reported patient symptoms, supplemented by an electrocardiogram or any form of documented long-term rhythm monitoring such as a cardiac event or a Holter monitor. A three-month blanking period was used post ablation to allow for recurrence of atrial fibrillation after the initial procedure with the exception for symptomatic patients with early recurrence that required electrical cardioversion or repeat ablation.
Statistical analysis:

We reported continuous variables as mean with standard deviation and categorical variables as frequency and percentage. A multivariable Cox proportional hazard model was used to assess if ACEi or ARB treatment predicted the risk of AA recurrence. For the multivariate analysis, we utilized two models. In the first model analysis was adjusted for non-modifiable variables including age and gender. In the second model analysis was adjusted for both non-modifiable (Model 1) and modifiable variables including diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease (CAD), heart failure (HF), chronic kidney disease stage 3 or higher, and at least moderate degree of any valvular heart disease. The Chi-square test was used to analyze the significance of the categorical variables and the student t-test was used to analyze the significance of continuous variables. To look for the association between ACEi / ARB use and the recurrence of AA we used the multivariable Cox- proportional analysis and calculated hazard ratio (HR) and 95% confidence intervals (CI). We used Kaplan-Meier method to obtain survival curve and log-rank test for their comparison. SAS version 9.4 (SAS Institute Inc, Cary, NC) was used for all these statistical analyses. To be significant the p-values had to be < 0.05.

RESULTS

Between January 2015 and April 2018, 103 patients undergoing CBA as a first or repeat procedure for paroxysmal AF, were identified and included in this study. They were divided into two groups based on the use of ACEi/ARBs at the time of CBA. Their baseline characteristics are presented and compared in Table 1. Out of the 103 patients, 42 patients were receiving ACEi/ARBs at the time of CBA. The mean age was similar in both groups (61.7±8.6 years in the ACEi/ARB group vs. 59.9±9.5 years in the other group). Patients in the ACEi/ARB group were more likely to be male (78.6% vs. 65.6%), hypertensive (86% vs. 54.1%) with CAD (26.2 vs. 9.8%). Out of the 42 patients, 21 (58%) patients were on ACEi and 15 (42%) were on ARB. In the ACEi group, all (100%) of the patients were taking Lisinopril. In the ARB group, 87% of patients were taking
Losartan. The mean dose for lisinopril was 16 mg orally daily and the median dose was 10 mg orally daily. For patients taking Losartan, the mean and median dose were 57 mg and 50 mg orally daily, respectively.

At one-year follow-up, 19 (8.4%) participants developed recurrence of AA (Figure 1). The role of ACEi and ARB in preventing the recurrence of AA following CBA for paroxysmal AF was assessed using a multivariable Cox proportional hazard model (Table 2). In the initial model adjusted for age and sex, ACEi/ARB use did not have a significant impact on AA recurrence after CBA for paroxysmal AF (HR 1.78, 0.72-4.42, p=0.66). In a second model adjusted for CAD, congestive HF, diabetes mellitus, hypertension, and valvular heart disease, ACEi/ARB use still did not have a significant impact on AA recurrence after CBA for paroxysmal AF (HR 1.37, 0.51-3.7, p=0.72). On Kaplan-Meier analysis, ACEi/ARB use did not predict the time to first recurrence of AA (Figure 2, p=0.2173) in these patients.

**DISCUSSION**

In paroxysmal AF patients undergoing CBA, the use of pre-procedural ACEi or ARB had no effect on the recurrence of AA at a one year follow up period. To our knowledge, this study is the first of its kind which has examined the effect of ACEi/ARB use in this exclusive subset of patients. It is important to note, that the ACEi/ARB group of patients that underwent CBA for paroxysmal atrial fibrillation had significantly higher prevalence of HTN and CAD that are known to contribute to myocardial fibrosis. Additionally, both hypertension and CAD contributed to increased left ventricular compliance and left atrial (LA) filling pressure. Subsequent LA enlargement further promotes AA. These comorbidities, however, were adjusted for in multivariate analysis in Model 2 shown above.

The pulmonary veins are the most common substrate for AF initiation.10 Isolated firing of the atrial myocardium can lead to AF initiation initially as an ectopic focus.
subsequently progressing to a single-circuit re-entry, and eventually to a multiple-circuit re-entry.11,12 The process correlates with the duration of AF as it progresses from paroxysmal to persistent, and eventually permanent AF. Myocardial remodeling is one of the key factors in the pathophysiology of AF and is defined as a group of molecular, cellular, and interstitial changes that clinically manifest as changes in size, shape, and function of the heart resulting from cardiac injury.13 Additionally, myocardial remodeling can be classified into electrical and structural remodeling which in turn can be physiological (adaptive) or pathological.14 There are several ways in which remodeling could lead to arrhythmia development. The first mechanism involves ion channel changes such as inactivation of sodium ion channels, changes in calcium and potassium ion channels, and alteration in the sodium/calcium exchanger function.5,15–17 Another mechanism includes changes in the junctional intercellular communication, particularly in protein connexin that is responsible for contact between adjacent cells and electrical coupling.18 Finally, there is structural cardiac remodeling that involves cell death and fibroblast proliferation that promotes extracellular matrix production, and, eventually, fibrosis.19,20 Fibrotic lesions impede electrical propagation and eventually promote mechanisms for re-entrant arrhythmias.14

In recent times, there has been a renewed interest in investigating the role of the renin angiotensin aldosterone system (RAAS) in AF. There are several ways hypothesized in which ACEi and ARBs can potentially affect clinical outcomes. These drugs not only have direct effects on the functional remodeling or electrical properties but also indirect effects by controlling hypertension and HF symptoms which are known risk factors for AF.21 Atrial myocardium is sensitive to increased hemodynamic stressors due to volume and pressure overload from hypertension and HF. These stressors can in turn promote electrical alterations such as decreased resting potential and delayed afterdepolarizations contributing to increased myocardial excitability.22 Additionally, increased hemodynamic load and myocardial mechanical stretch can activate genetic pathways that rapidly augment the secretion of angiotensin II.23 Angiotensin II can
successively contribute to arrhythmogenicity by promoting an increase net inward calcium current in affected cardiomyocytes and by inducing myocardial hypertrophy and fibrosis. Increased fibrosis of the atrial myocardium is known to be associated with AF. G protein-coupled receptor agonists like angiotensin II induce cellular differentiation processes and activation of fibroblasts, and the development of interstitial fibrosis through activation of extracellular signal-regulating kinases (Erk). These findings were confirmed in a small study by Goette et. al. where patients with AF undergoing cardiac surgery were found to have a significant increase in atrial fibrosis along with an increased expression of Erk1 and Erk2 in atrial interstitial cells.

The use of ACEi and ARB has also been shown to be associated with a decreased AF burden in certain population groups. Anné et.al. investigated 196 patients undergoing RF ablation for atrial flutter and evaluated outcomes associated with the use of an ACEi and ARB. Predictably, more than half of these patients eventually developed AF, but it was found that the use of an ACEi/ARB was associated with reduced incidence of AF post atrial flutter ablation (p=0.04). Furthermore, the use of ARBs was evaluated in conjunction with antiarrhythmic medications and showed better outcomes in comparison to anti-arrhythmics alone. In a prospective randomized trial by Madrid et.al., 159 patients were randomized to either amiodarone or amiodarone plus irbesartan group to evaluate the role of ACEi in maintaining sinus rhythm in persistent AF. Patients in the irbesartan plus amiodarone combination group had a statistically significant higher rate of sinus rhythm maintenance at 360 days in comparison to the group on amiodarone alone.

In patients with HF and AF, pre-ablation use of an ACEi resulted in an improved ablation success rate in non-paroxysmal AF with low ejection fraction. In a single-center, Mohanty et. al. investigated 703 consecutive patients with preserved left ventricular ejection fraction (LVEF >45%) and 345 patients with reduced EF (<45%) undergoing RF ablation for AF. At 24 ± 7 months of follow up, in patients with non-
paroxysmal AF and reduced EF, the ACEi pre-treatment group had lower recurrence of AF post RF ablation compared to the non-ACEi group (76% vs 64%, p=0.015). Among paroxysmal AF patients regardless of LVEF, ACEi use was not observed to be associated with improved RF ablation outcomes (80% vs 77%, P = 0.82). These findings are similar to our study which demonstrated that in patients with paroxysmal AF the use of an ACEi or an ARB did not affect outcomes and event-free survival following CBA. Currently, the guidelines do not recommend the use of ARB or ACEi for the sole purpose of preventing the recurrence of AF due to a lack of substantial literature supporting it. However, there is growing evidence that in patients with non-paroxysmal AF undergoing RF ablation, the use of ACEi and ARB decreases the recurrence of AF.

Our study is not without its inherent limitations. Firstly, we are a single center retrospective study with a smaller sample size limiting the generalizability of outcomes. Secondly, the study population is underpowered for the detection of benefits in patients with paroxysmal AF. Thirdly, we examined an exclusive population of patients with paroxysmal AF and not persistent AF which are known to have a higher degree of electrical and structural remodeling with the potential for superior benefits with ACEi/ARB use. Furthermore, since this was a small sample retrospective study, we could not perform a power analysis. Lastly, our patient population within the ACEi/ARB group had a higher rate of HTN and CAD. Although these factors were accounted for in the multivariate analysis, we did not collect the data on whether CAD was optimally treated or required a revascularization procedure. Despite these limitations, our study is a first of its kind to examine the role of ACEi/ARB use in an exclusive population of paroxysmal AF patients undergoing CBA.

CONCLUSION:
In paroxysmal AF patients undergoing CBA, the use of ACEi or ARB was not associated with decreased recurrence of AA. Larger, multicenter, controlled studies, particularly in
patients with persistent AF and those at risk for significant myocardial fibrosis such as cardiomyopathy, HF or valvular disease are necessary to fully evaluate the effect of ACEi, ARB or angiotensin receptor neprilysin inhibitor (ARNI) such as sacubitril/valsartan in patients undergoing CBA for AF.

**Funding Source:** There was no funding for this study.

### Compliance with Ethical Standards

**Conflict of interest:** The authors declare they have no conflict of interest.  **Ethical approval:** The study was approved by the institutional review board for our institution. Since this was a retrospective chart review, no studies or interventions were performed on animals or humans.

### ARTICLE HIGHLIGHTS

**Research background**

Cryo-balloon ablation (CBA) therapy is recommended for patients with paroxysmal AF refractory to anti-arrhythmic drugs. However, only 80% of patients benefit from an initial CBA.

**Research motivation**

Myocardial fibrosis is a known risk factor for the development of AF and angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are known agents that prevent remodeling. There is growing evidence that pretreatment with ACEi and ARB decreases the recurrence of AF post ablation, particularly in non-paroxysmal AF undergoing radiofrequency (RF) ablation.

**Research objectives**
we aimed to investigate the role of ACEi and ARB in preventing the recurrence of atrial arrhythmias (AA) following CBA for paroxysmal AF

**Research methods**

We performed a single-center, retrospective, cross-sectional study. All patients aged 18 or older, with a diagnosis of paroxysmal AF, undergoing CBA as a first or repeat procedure between January 2015 and April 2018 were included in the study. We followed these patients with paroxysmal AF undergoing CBA for one-year post procedure. Recurrence was assessed by documented AA on EKG or any form of long-term cardiac rhythm monitoring.

**Research results**

After a one-year follow-up, out of 103 patients, 19 (18.4%) participants developed recurrence of AA. Of these 42 patients were receiving ACEi/ARBs at the time of CBA. 21 (58%) patients were on ACEi and 15 (42%) were on ARB. Patients on ACEi/ARB had a greater prevalence of hypertension and coronary artery disease. On a multivariate model adjusted for baseline demographics and risk factors for AF, ACEi or ARB therapy did not prevent the recurrence of AA following CBA ($P = 0.72$). Similarly, on Kaplan-Meier analysis pretreatment with ACEi/ARB did not predict the time to first recurrence of AA ($P = 0.2173$).

**Research conclusions**

In paroxysmal AF patients undergoing CBA, the use of ACEi or ARB was not associated with decreased recurrence of AA

**Research perspectives**

Future studies, particularly in patients with persistent AF and those at risk for significant myocardial fibrosis such as cardiomyopathy, HF or valvular disease are
necessary to fully evaluate the effect of ACEi, ARB or angiotensin receptor neprilysin inhibitor (ARNI) such as sacubitril/valsartan in patients undergoing CBA for AF.
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