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## Relationship of Ostial Pulmonary Vein Scar with Reduction in Pulmonary Vein Size after Radiofrequency Ablation for the Treatment of Atrial Fibrillation: An Observational Cohort Study

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## Abstract

**Background:** Radiofrequency (RF) ablation procedures to electrically isolate the pulmonary veins (PV) from the left atrium are frequently used to treat atrial fibrillation. We hypothesized that changes in PV size after RF ablation would correlate with the volume of ostial PV scar as assessed by high resolution late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR).

<u>Methods</u>: The study cohort included 23 consecutive subjects. Contrast enhanced PV CMR angiography and LGE were obtained before and 42 ± 18 days after RF ablation.

<u>Results:</u> A total of 85 PV were analyzed. Imaging after RF ablation demonstrated a reduction in PV diameter ( $22 \pm 7 \text{ mm}$  to  $21 \pm 6 \text{ mm}$ , p = 0.001) and a reduction in cross-sectional area (CSA) ( $285 \pm 141$  to  $246 \pm 110$ , p < 0.001). There was a significant correlation of PV ostial normalized scar volume with the change in PV diameter (r=-0.21, p =0.049) and CSA (r=-0.28, p =0.010) after AF ablation. PV in the highest quartile for PV scar had the greatest reduction in diameter and CSA (p <0.05 for both).

<u>Conclusion</u>: PV size decreases significantly after RF ablation for the treatment of AF. The change in PV size is linearly related to the quantity of LGE scar at the PV ostium.

## Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, resulting in significant morbidity and increased healthcare costs.<sup>1</sup> The recognition that the pulmonary veins (PV) play a critical role in the initiation and maintenance of AF<sup>2</sup> has led to the development of a variety of procedures that electrically isolate the PV from the left atrium and thus reduce the incidence of recurrent AF.<sup>3-7</sup> The vast majority of these procedures utilize radiofrequency (RF) ablation, resulting in scar around the PV ostium. PV stenosis is a rare but serious complication of the procedure<sup>8, 9</sup> that has

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been shown in animal studies to be related to PV scarring.<sup>10</sup> Reduction in PV size after RF ablation has been observed even in the absence of obvious stenosis and may be related to the intensity of ablation, a surrogate measure for the extent of scar.<sup>11</sup> Late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) directly visualizes myocardial scar in the left atrium and PV after the procedure.<sup>12</sup> Additionally, contrast enhanced CMR readily visualizes the PV anatomy and provides for reproducible anatomic measurements.<sup>13</sup> The relationship of ostial PV scar to changes in PV size after RF ablation has not previously been investigated.

We hypothesized that the change in PV size after RF ablation for the treatment of AF would correlate with the volume of ostial PV scar as assessed by high resolution LGE CMR. We evaluated this hypothesis in a consecutive cohort of 23 patients referred for CMR before and after RF ablation for the treatment of AF.

#### Material and Methods

#### Study Cohort

The study cohort comprised a consecutive series of

patients who underwent CMR before and after RF ablation for the treatment of AF. No subject had previously undergone PV isolation. All study subjects had an estimated glomerular filtration rate of >60 ml/min/1.73 m<sup>2</sup>. The study was reviewed and approved by the hospital Committee on Clinical Investigations (Institutional Review Board).

#### **CMR** Protocol

CMR was performed using a 1.5 T whole-body MR system (Achieva, Philips Medical Systems, Best, The Netherlands) with a five or sixteen element cardiac coil for RF signal reception.

First pass breath-hold 3D contrast enhanced CMR of the PV was obtained after injection of 0.2 mmol/kg gadopentetate dimeglumine (Gd-DTPA) (Magnevist ®, Berlex Laboratories, Wayne, NJ), immediately followed by a saline flush.<sup>13</sup> Data acquisition began after a delay determined by a small timing bolus given prior to contrast enhanced CMR. Two dynamics were acquired using an end-expiratory breath-hold spoiled 3D gradient echo sequence with the following parameters: repetition time 4.0 ms, echo time 1.3 ms, flip angle 30 degrees, 50 slices, slice thickness 3 mm interpolated to 1.5 mm,

**Figure 1:** Methodology for Measuring Scar Volumes. Late Gadolinium Enhancement (LGE) Images Demonstrate Hyperenhancement/scar in the Left Inferior Pulmonary Vein (LIPV) and the Right Inferior Pulmonary Vein (RIPV) (A). The Extent of Scar is Determined using Signal Thresholding with Scar Highlighted in Red (B). A Region of Interest (ROI) is Used to Identify Scar on Each Slice as Belonging to one of the PV, with the LIPV ROI Shown (C). Each PV in Each Slice is Analyzed using Thresholding and ROIs to Identify Scarred Pixels in each Region (D). Total Scar is Summed Over all Slices (E). From Peters et al, JACC Cardiovasc Imaging 2009, 2:308-316 [15], used with Permission



field of view 360 mm, matrix 256 x 256, imaging time 11 s per dynamic. The 3D volume was centered on the left atrium and included all PV. Images were prospectively acquired in the axial plane.

High-resolution LGE CMR was obtained 20 to 25 min after contrast administration. Images were acquired using a fat suppressed, ECG triggered, navigator gated 3D inversion recovery gradient echo using the following parameters: repetition time 4.4 ms, echo time 2.1 ms, flip angle 20 degrees, average inversion time 280 ms, slice thickness 5 mm, field of view 320 mm, matrix 224 x 224, spatial resolution  $1.4 \times 1.4 \times 5$  mm, imaging time 4 to 8 minutes (depending on navigator efficiency).<sup>12</sup>

CMR of the left ventricle and left atrium was performed in the 2-chamber, 4-chamber, and contiguous short axis orientations with a standard breath-held balanced steady-state free-precession sequence.<sup>14</sup>

#### Image Analysis

All image analyses were performed by observers blinded to the patient clinical treatment data.

Commercially available system software (View-

Forum, Philips Medical Systems, Best, The Netherlands) was used to generate multiplanar reformations of the contrast enhanced CMR images. The maximum diameter and cross-sectional area (CSA) of the PV were measured at the location in the sagittal plane at which the PV separated from the left atrium and from each other.<sup>13</sup> A left common PV was defined as a single left-sided PV entering the left atrium as determined in the sagittal plane. A right middle PV was defined as any right-sided pulmonary vein identified in the sagittal plane in addition to the right inferior and right superior PV. The change in size (diameter and CSA) of the PV after ablation was determined as a percent of the baseline measurement.

LGE CMR images were analyzed in Matlab 7.1 (Mathworks, Natick, Massachusetts). The volume of scar at the ostium of the PV was determined by a threshold technique,<sup>15</sup> determined as 3 standard deviations of noise added to the signal of the blood pool. After thresholding, isolated high signal intensity voxels were removed. The scar was segregated into regions adjacent to each of the PV ostia (Figure 1). The quantity of scar was normalized to the CSA of the PV to account for variability in PV size.

Left atrial length was measured in the 4-chamber view at its maximal size over the cardiac cycle. Left atrial volume was determined using the arealength method from data in the 2-chamber and

Table 1 Characteristics of the Study Cohort	
Study Cohort Characteristics (N = 23)	Mean ± SD
Male (N, %)	20 (87%)
Age (years)	58 ± 13
Height (inches)	$71 \pm 4$
Weight (pounds)	198 ± 35
Paroxysmal atrial fibrillation (N, %)	18 (78%)
Mitral regurgitation: None (N, %)	15 (65%)
Mild (N, %)	5 (22%)
Moderate (N, %)	3 (13%)
Hypertension (N, %)	7 (30%)
Coronary artery disease (N, %)	4 (17%)
Obstructive sleep apnea (N, %)	3 (13%)
Hypertrophic cardiomyopathy (N, %)	2 (9%)
Congestive heart failure (N, %)	1 (4%)
Diabetes mellitus (N, %)	1 (4%)

4-chamber views. Left ventricular volumes and ejection fraction were determined in the short axis orientation using the method of disk summation.<sup>14</sup> Volume measures were indexed to the body surface area.

#### Atrial Fibrillation Ablation

The AF ablation was performed using a femoral venous approach as described in detail elsewhere.<sup>4</sup> A decapolar catheter was positioned in the coronary sinus and a second catheter was placed in the right atrium. Left atrial access was obtained by two transseptal punctures. Transesophageal or intracardiac echocardiography was used throughout the procedure to assist in transseptal puncture and to monitor catheter position during ablation. Three-dimensional electroanatomic mapping of the left atrium and PV was performed using a non-irrigated 8 mm or externally irrigated 3.5 mm NaviStar<sup>™</sup> catheter (Biosense Webster, Diamond Bar, CA) and CARTO<sup>™</sup> (Biosense Webster) and/ or EnSite NavX<sup>TM</sup> (Endocardial Solutions, St. Paul, MN) mapping systems. Electrograms were recorded during sinus rhythm, coronary sinus pacing, or AF at the ostia of the PV with a 10-20 pole circumferential catheter with distal ring configuration (Biosense Webster or Bard, Covington, GA). Radiofrequency ablation was performed outside the PV ostia near sites with the earliest PV electrograms. Radiofrequency ablation was targeted in the antrum, approximately 1 cm from the PV ostium, with additional carinal lesions depending on the response to the antral ablation. Ablation was

performed for 20-60 seconds with a target temperature of 52 degrees C for non-irrigated catheters and with a maximum power of 30 watts and maximum temperature of 42 degrees C for irrigated catheters. The process was repeated until complete bi-directional electrical PV isolation was achieved, defined by both entrance block as demonstrated by loss of PV potentials, and exit block demonstrated by failure to capture the left atrium during sinus rhythm by pacing (at 10 mA and 2 ms pulse width) each of the bipolar pairs of electrodes of the circumferential catheter positioned at the entrance of the PV. All PV were routinely isolated for all patients. After PV isolation, induction of AF was attempted by burst pacing from the right atrium and coronary sinus before and after administration of isoproterenol. Isolation of the PV was reassessed at least 30 minutes after ablation and if reconnection was observed the vein was re-isolated. Additional ablation lines in the left atrium were not routinely performed.

#### Statistical Analysis

Data are presented as counts and percentages or mean ± standard deviation as appropriate. Measurements before and after RF ablation were compared using a paired T test. The relationship of changes in PV size to the volume of PV scar was assessed using standard correlation and linear regression. PV were also segregated into quartiles based on the volume of ostial scar and compared using analysis of variance. The Student-Newman-Keuls adjustment for post-hoc comparisons was

	Pre-Ablation	Post Ablation
Pulmonary vein diameter (mm)	22 ± 7	$21 \pm 6^*$
CSA (mm <sup>2</sup> )	$289 \pm 140$	$246 \pm 110^{*}$
Scar (ml)		$2.1 \pm 1.3$
Normalized scar (m <sup>1</sup> /mm <sup>2</sup> )		$0.010 \pm 0.009$
Left ventricular ejection fraction (%)	59 ± 8	$60 \pm 8$
Left ventricular end diastolic volume index (ml/ m <sup>2</sup> )	80 ± 20	86 ± 19†
Left ventricular mass index (g/m <sup>2</sup> )	$67 \pm 24$	$68 \pm 27$
Left atrial 4-chamber dimension (mm)	$59 \pm 11$	$58 \pm 6$
Left atrial volume index (m <sup>1</sup> /m <sup>2</sup> )	58 ± 21	$60 \pm 22$

CMR Measurements before and After the Ablation Procedure

CSA = cross sectional area, \*p ≤0.001 compared to pre-ablation, †p <0.01 compared to pre-ablation

Table 2

used to identify significant differences between ( quartiles. A p-valueof <0.05 was used to determine statistical significance. All statistical analyses were performed using SAS for Windows 9.1 (SAS Institute, Cary, NC).

### Results

#### Study Cohort

The clinical characteristics of the study cohort are summarized in Table 1. The cohort was predominantly men and most had paroxysmal AF. The left sided PV had a common origin in 5 subjects. Six small right middle PV and a small right accessory PV were not included in the analysis. Scar could not be assessed in one PV due to image artifacts. A total of 85 PV were therefore available for analysis.

# Changes in Cardiac Anatomy after RF Ablation

Imaging was performed before and  $42 \pm 18$  days after RF ablation (Table 2). PV diameter and CSA were significantly reduced after the procedure

(p <0.001 for both). There was no scar visualized on images performed prior to the procedure. After ablation, extensive scar involving more than 3 quadrants of the PV was present in 44 (52%), minimal scar involving 1 quadrant of the PV or less was present in 10 (12%), and intermediate scar was present in 31 (36%). Left atrial size and left ventricular ejection fraction and mass were unchanged.

# Relationship of Changes in PV size to Scar Volume

There was a significant linear relationship between the change in PV size and the scar volume normalized for the PV CSA, with a stronger relationship for the PV CSA (PV diameter: r = -0.21, p = 0.049; PV CSA: r = -0.28, p = 0.010; Figures 2 and 3). The PV in the highest quartile of normalized scar volume had significantly greater reductions in both maximum diameter and CSA (p <0.5 for both comparisons, Figure 4).

#### Discussion

In this cohort of 23 consecutive patients with AF undergoing CMR before and after RF ablation, we

**Figure 2:** Left Inferior Pulmonary Vein (LIPV) Before and After Radiofrequency (RF) Ablation. Before RF Ablation, the LIPV has Normal Size (A, dimension shown) with Contrast Enhanced Cardiovascular Magnetic Resonance (CMR) and Absence of Scar with Late Gadolinium Enhancement (LGE) (B). The Right Inferior Pulmonary Vein (RIPV) is also Shown. After RF Ablation, the Size of the Left Inferior PV is Reduced (C, dimension shown) and Scar is Apparent as Increased Signal in the Wall of the LIPV (D)



found that the there was a small but significant reduction in PV size after RF ablation for the treatment of AF and that this reduction was related to the volume of ostial PV scar as defined by LGE CMR.scar. There was a significantly greater reduction in size for those PV that have the largest amount of scar. This study directly demonstrates for the first time in humans that scarring after RF ablation correlates with a reduction in PV size.

AF is the most common sustained cardiac arrhythmia, affecting more than 2 million people in the United States.<sup>1,16</sup> AF is a major cause of morbidity, increasing the risk of stroke by a factor of 5 and accounting for 15% of all strokes.<sup>1</sup> A major breakthrough in our understanding of the pathophysiology of AF was the recognition that ectopic activity in the PV plays a critical role in the initiation and maintenance of AF.<sup>2</sup> This led to the development of RF ablation procedures to electrically isolate the PV to prevent recurrent AF.<sup>3-7</sup> Shortterm success rates for these procedures range from 65% to 85% in patients with paroxysmal AF, with a reduction in morbidity and improved quality of life.<sup>17</sup> PV stenosis is an uncommon but severe complication of RF ablation for the treatment of AF.8,9 In animal studies, application of RF energy to the PV causes intimal proliferation and myocardial necrosis that can result in stenosis or occlusion.<sup>10</sup> Severe stenosis occurs in up to 5% of patients after the procedure.9 Reductions in PV size have been observed even in the absence of severe stenosis.<sup>11,18</sup> The mechanism for this reduction has been uncertain. One study demonstrated a significant relationship between reduction in PV size and surrogate markers for the extent of scarring (circumferentiality of PV ablation), suggesting that PV scarring is responsible.<sup>11</sup> Other studies have found no relationship between these surrogate markers and reduction in PV size, suggesting the possibility that reductions in PV size may be related to hemodynamic changes with the restoration of sinus rhythm.18-20

We found that reductions in PV size after RF ablation are associated with the volume of PV ostial scar as defined by LGE CMR. This suggests that PV scarring plays the major role in the reduction of PV size after RF ablation. The variability of pri-

**Figure 3:** Volume Rendered Image Showing Extent of Scar Relative to the Pulmonary veins. Scar, as Determined by LGE, is Shown in Red



or studies attempting to address the role of scarring in this setting may be due to the inadequacy of using surrogate measures of scar compared to a direct measurement.

We found that reduction in PV size was most evident in those veins that had the most scar, while there was minimal change in those PV with minimal scar. This suggests that the PV may be able to tolerate scarring up to a threshold beyond which further scarring causes a reduction in PV size. Identification of a consistent threshold level across patients may be able to identify a maximum intensity of RF ablation that can be safely applied without significant alteration of PV size. This hypothesis requires a larger study population to for evaluation.

The relationship between ostial PV scar and reductions in PV size were most significant for PV CSA. Although most investigators have reported only PV diameters, these single dimension measurements of an asymmetric structure have suboptimal reproducibility due to variations in PV anatomy such that measurements of PV diameter in different planes can result in significantly different results.<sup>21</sup> CSA measurements are less dependent on the plane of measurement and more reproducible.<sup>13</sup>

Our study has several limitations. Though consecutive, the sample size was small. Replication in a larger cohort would increase the confidence in the study results. The study cohort was predominantly men with paroxysmal AF and conducted at a tertiary care academic medical center. The results may not be generalizable to other populations. The relationship of PV scar and changes in size after ablation may vary depending on the technique used. In particular, wide area catheter ablation techniques may result in more scar due to extensive ablation but less change in PV size due to the placement of the lesions away from the PV ostia, although the volume of scar may be less than anticipated because of the relative thinness of the posterior wall.

**Figure 4:** The Linear Relationship (solid line) and 95% Confidence Intervals (dashed line) of Normalized Ostial PV Scar Volume with the Difference in PV Diameter (A) and Cross-Sectional Area (CSA) (B) Before and After RF Ablation for the Treatment of AF. The Linear Relationship is Statistically Significant for Both the Diameter (p =0.049) and the CSA (p =0.010)



**Original Reasearch** 

**Figure 5:** The Relationship of Normalized Ostial PV Scar Quartile with the Change in PV Diameter and CSA. The Group with the Highest Quartile of Normalized PV Scar had the Greatest Reduction in Size



## Conclusions

PV size decreases after RF ablation for the treatment of AF. The change in PV size has a significant relationship with the quantity of ostial PV scar.

## Disclosures

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