Atrial Fibrosis Quantified Using Late Gadolinium Enhancement MRI is Associated With Sinus Node Dysfunction Requiring Pacemaker Implant

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Atrial Fibrosis and Sinus Node Dysfunction. ***Introduction:*** **Sinus node dysfunction (SND) commonly manifests with atrial arrhythmias alternating with sinus pauses and sinus bradycardia. The underlying process is thought to be because of atrial fibrosis. We assessed the value of atrial fibrosis, quantified using Late Gadolinium Enhanced-MRI (LGE-MRI), in predicting significant SND requiring pacemaker implant.**

Methods: **Three hundred forty-four patients with atrial fibrillation (AF) presenting for catheter ablation underwent LGE-MRI. Left atrial (LA) fibrosis was quantified in all patients and right atrial (RA) fibrosis in 134 patients. All patients underwent catheter ablation with pulmonary vein isolation with posterior wall and septal debulking. Patients were followed prospectively for 329 ± 245 days. Ambulatory monitoring was instituted every 3 months. Symptomatic pauses and bradycardia were treated with pacemaker implantation per published guidelines.**

Results: **The average patient age was 65 ± 12 years. The average wall fibrosis was 16.7 ± 11.1% in the LA, and 5.3 ± 6.4% in the RA. RA fibrosis was correlated with LA fibrosis ($R^2 = 0.26$; $P < 0.01$). Patients were divided into 4 stages of LA fibrosis (Utah I: <5%, Utah II: 5–20%, Utah III: 20–35%, Utah IV: >35%). Twenty-two patients (mean atrial fibrosis, 23.9%) required pacemaker implantation during follow-up. Univariate and multivariate analysis identified LA fibrosis stage (OR, 2.2) as a significant predictor for pacemaker implantation with an area under the curve of 0.704.**

Conclusions: **In patients with AF presenting for catheter ablation, LGE-MRI quantification of atrial fibrosis demonstrates preferential LA involvement. Significant atrial fibrosis is associated with clinically significant SND requiring pacemaker implantation.** *(J Cardiovasc Electrophysiol, Vol. 23, pp. 44-50, January 2012)*

atrial fibrillation, catheter ablation, magnetic resonance imaging, pacemaker, sinus node dysfunction

Introduction

Tachycardia–bradycardia syndrome is a common manifestation of sinus node dysfunction (SND) in patients with atrial fibrillation (AF). This syndrome consists of periods of tachycardia, commonly AF or atrial flutter, which terminates into sinus rhythm, often with prolonged pauses because of prolonged sinus node recovery times, sinoatrial conduction time, and symptomatic sinus bradycardia. The latter are common indications for permanent pacing in patients with AF.[1]

The association of SND and AF has long been demonstrated; however, its underlying mechanism is not clearly understood. SND has been demonstrated in animal models of pacing-induced AF, as indicated by prolonged sinus node recovery time and intra-atrial conduction time.[2] In humans with atrial flutter, sinus node recovery time was significantly improved 3 weeks following catheter ablation of this arrhythmia.[3] In patients with SND undergoing catheter ablation for AF, sinus pauses were eliminated off of antiarrhythmic and rate controlling drugs.[4] The sinus node is a complex structure with a diverse activation pattern and multiple exit sites.[5] Atrial arrhythmia-induced electrical remodeling is accompanied by structural remodeling that affects the sinus node. Autopsy studies have demonstrated degenerative fibrosis involving nodal and nodal–atrial continuity in patients with SND.[6]

Late Gadolinium Enhancement MRI (LGE-MRI) is emerging as a noninvasive method of assessment of ventricular and atrial structural tissue remodeling or fibrosis.[7,8] Recently, we demonstrated the use of this technique in staging left atrial (LA) fibrosis and predicting response to catheter ablation in patients with AF. In this study, we sought in addition, to evaluate right atrial (RA) tissue structural remodeling using LGE-MRI. We also used LGE-MRI to assess the role of atrial fibrosis in predicting significant SND requiring pacemaker implantation following catheter ablation of AF. Our hypotheses are that (1) AF-associated atrial fibrosis also affects the right atrium, and that (2) advanced atrial fibrosis is associated with significant SND requiring permanent pacing.

Dr. Marrouche holds IP on the CoreView software used in the study. Other authors: No disclosures.

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Methods

This is an observational study, which included 344 patients with AF presenting to the University of Utah between November 2006 and November 2009. Patient information gathered for the purposes of the study was de-identified and protected in compliance with the Health Insurance Portability and Accountability Act (HIPAA) regulations. All patients underwent delayed enhancement MRI evaluation preablation to assess the extent of atrial tissue fibrosis.

MRI Image Acquisition

LGE-MRI scans were obtained on either a 1.5 Tesla Avanto or a 3.0 Tesla Trio clinical scanners (Siemens Medical Solutions, Erlangen, Germany) using a total imaging matrix (TIM) phased-array receiver coil. The scan was acquired 15 minutes following contrast agent injection (0.1 mmol/kg, Multihance [Bracco Diagnostic Inc., Princeton, NJ, USA]) using a 3-dimensional (3D) inversion recovery, respiration navigated, electrocardiogram (ECG)-gated, gradient echo pulse sequence. Typical acquisition parameters were: free-breathing using navigator gating, a transverse imaging volume with voxel size = $1.25 \times 1.25 \times 2.5$ mm (reconstructed to $0.625 \times 0.625 \times 1.25$ mm), reception time/echo time (TR/TE) = 5.4/2.3 milliseconds, flip angle = 20^{o}, inversion time (TI) = 270–310 milliseconds, and GRAPPA with R = 2 and 46 reference lines. ECG gating was used to acquire a small subset of phase encoding views during the diastolic phase of the atrial cardiac cycle. The time interval between the R-peak of the ECG and the start of data acquisition was defined using the cine images of the atria. Fat saturation was used to suppress fat signal. The TE of the scan (2.3 milliseconds) was chosen such that fat and water were out of phase and the signal intensity of partial volume fat-tissue voxels was reduced allowing improved delineation of the atrial wall boundaries. The TI value for the LGE-MRI scan was identified using a scout scan. Typical scan time for the LGE-MRI study was 5–10 minutes depending on subject respiratory and heart rate.

LGE-MRI Quantification of Preablation Fibrosis

After successful acquisition of a good quality LGE-MRI using the above-mentioned sequences, the CoreView software (MARREK Inc., Salt Lake City, UT, USA) was used to quantify atrial fibrosis within the atrial myocardium. Figure 1 demonstrates an example of an acquired LGE-MRI with 3D reconstruction demonstrating fibrosis in right and left atria. Commensurate with our previous publications,[9] we then divided the 343 patient cohort into 4 groups corresponding to 4 stages of LA fibrosis as follows: Utah stage 1 or minimal fibrosis (less than 5% enhancement), Utah stage 2 or mild fibrosis (5–20% enhancement), Utah stage 3 or moderate fibrosis (20–35% enhancement), and Utah stage 4 or extensive fibrosis (greater than 35% enhancement).

Ablation Procedure

The details and our approach to the ablation procedure (pulmonary vein isolation in addition to posterior wall and septal debulking) have been described elsewhere.[10] In brief, the left atrium was accessed through 2 transseptal punctures under intracardiac echo guidance using a phased array catheter (Acunav; Siemens Medical Solutions USA Inc., Mountain View, CA, USA). A 10-pole circular mapping catheter (Lasso; Biosense Webster, Diamond Bar, CA, USA) and a 3.5-mm Thermocool ablation catheter (Biosense Webster) were advanced into the left atrium for mapping and ablation. A 14-pole catheter (TZ Medical, Portland, OR, USA) was used to record RA and coronary sinus electrograms and was used as the reference catheter for 3D electroanatomical mapping with CARTO (Biosense Webster). Radiofrequency energy was delivered from a 3.5 mm Biosense Webster Thermocool irrigated tip catheter. Ablation parameters were 50 watts at 50 °C for 5 seconds, guided by electrogram abolition recorded on the Lasso catheter. Ablation lesions were placed in a circular fashion in the pulmonary vein antral region until electrical isolation of the pulmonary veins was achieved. Additional lesions were placed along the LA posterior wall and septum. Fifty-two patients (15.2%) with clinically manifested typical RA isthmus-dependent flutters also underwent linear ablation of the cavotricuspid isthmus where bidirectional block was achieved. No ablation in the superior vena cava region was performed in any of the patients in this study.

Follow-Up

A postablation blanking period was observed for 3 months during which all patients received an 8-week automatic trigger cardiac event monitor for assessment of early AF recurrence. Early recurrences were treated with direct current cardioversion, antiarrhythmic drugs (AADs), or both. AADs were discontinued at the end of the blanking period. All patients were seen in follow-up at 3 months following ablation and at 3-month intervals thereafter. Each patient received a 12-lead ECG and an 8-day Holter monitor for detection of arrhythmia recurrence postblanking. Additional ECG recordings were obtained as suggested by the patients' reported symptoms through weekly telephone calls. Recurrence was defined as any atrial arrhythmia sustained for longer than 30 seconds without antiarrhythmic drug treatment following the 3 months blanking period, as suggested by the Heart Rhythm Society (HRS) consensus statement.[11] All ablation procedures were performed on therapeutic anticoagulation with warfarin, which was continued postprocedure to maintain an international normalized ratio of 2.0–3.0.

Indications for Pacemaker Implantation

Patients with symptoms suggestive of SND, including symptomatic bradycardia, sinus pauses detected on ambulatory monitoring, and evidence of chronotropic incompetence were evaluated and implanted with dual chamber pacemakers per published guidelines.[1]

Data Analysis

Statistical analysis was performed using STATA 11 (StataCorp, College Station, TX, USA). Continuous variables are reported as means and standard deviations and categorical variables are reported as percentages of the cohort. Student's *t*-test was used to compare continuous variables and chi-square test to compare proportions. A multivariate logistic regression model reporting odds ratios (OR) was used to determine significant predictors of pacemaker implantation following ablation. To avoid overfitting, nonsignificant predictor variables were removed from the regression model in a stepwise fashion. Two-sided P values <0.05 were considered significant.

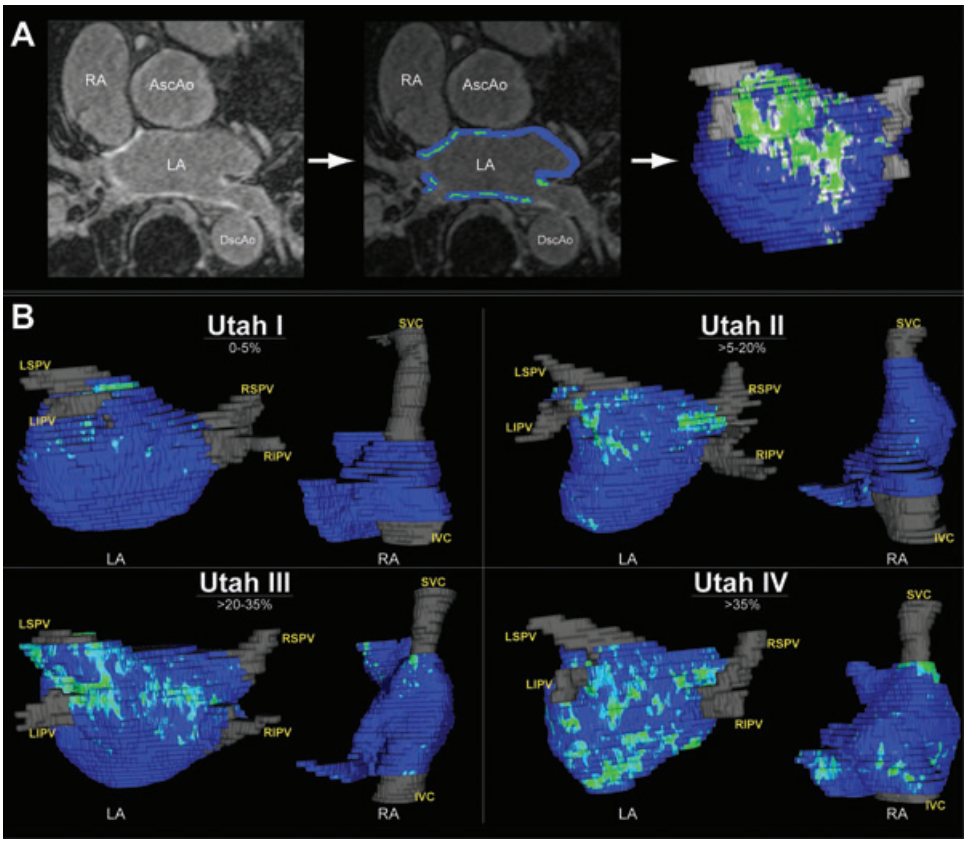

Figure 1. *MRI acquisition and quantification of atrial fibrosis—2-dimensional MRI illustrating the right and left atrial chambers and 3-dimensional color reconstructions of the left and right atria of 4 sample patients from the 4 Utah stages of fibrosis. The green color overlaid on a blue background corresponds to areas of atrial fibrosis.*

Results

Preablation Fibrosis/Structural Remodeling-Based Staging

Quantification of preablation fibrosis of the left atrium was obtained in all 344 patients. Fibrosis was quantified as a percentage of the atrial wall volume. In the left atrium, the average preablation fibrosis was $16.7 \pm 11.1\%$ ($N = 344$). Of the 344 patient cohort, 21 (6%) were in Utah stage 1, 221 (64%) in Utah stage 2, 78 (23%) in Utah stage 3, and 24 (7%) in Utah stage 4. Patients with advanced LA fibrosis stages (Utah stage 3 and Utah stage 4) had a higher average age, a higher prevalence of the female gender as well as a higher prevalence of persistent AF. The prevalence of hypertension, coronary artery disease, congestive heart failure, diabetes, and left ventricular ejection fraction were comparable across the 4 Utah stage groups. Patient characteristics are detailed in Table 1.

Quantitative Assessment of Right Atrial Fibrosis

Of the total 344 patient cohort, LGE-MRI quantification of RA fibrosis was performed in 134 patients. The average RA fibrosis was $5.4 \pm 6.1\%$. This was significantly lower than LA fibrosis ($P < 0.05$), suggesting that the structural remodeling process involves the left atrium more severely than the right atrium. Patients with more advanced stages of LA fibrosis had a higher degree of RA fibrosis. Linear regression analysis demonstrated RA fibrosis to be correlated with LA fibrosis stage ($r = 0.51$; $P < 0.01$; Fig. 2).

Qualitative Assessment of Right Atrial Fibrosis

RA 3D reconstructions were used to assess the location of fibrosis. Figure 3 demonstrates the spectrum of RA fibrosis in 3 AF patients. As shown, the majority of RA enhancement involves the septal region that is shared with the left atrium with relative sparing of the remainder of the right atrium. With advanced RA fibrosis, the enhancement pattern becomes more diffuse and extends laterally to the RA free wall, as well as vertically toward the vena cava junctions. As a group, patients with pacemakers implanted had more fibrosis visualized around the SVC-RA junction, correlating anatomically to the sinus node region.

Arrhythmia Recurrence

Over an average follow-up period of 329 ± 245 days, 102 patients (29.7%) experienced recurrent atrial arrhythmia as defined by the HRS consensus document definition.[11] Analyzed over the stages of fibrosis, only 1 patient in Utah stage 1 experienced recurrence (4.8%), 55 patients in Utah stage 2 (24.88%), 28 patients in Utah stage 3 (35.9%) and 19 patients in Utah stage 4 (79.2%). The preablation stage of LA fibrosis was the strongest predictor of recurrence, (hazard ratio, 1.96; $P < 0.01$) consistent with our previous publications.[8]

TABLE 1

Baseline Characteristics of 344 Patients Presented in Stages of Left Atrial Fibrosis

	Utah Stage 1 (<5% fibrosis) (N = 21)	Utah Stage 2 (5–20% fibrosis) (N = 221)	Utah Stage 3 (20–35% fibrosis) (N = 78)	Utah Stage 4 (>35% fibrosis) (N = 24)	P value
Age (years)	63 ± 13	64 ± 12	66 ± 13	72 ± 8	0.006
Gender (% male)	68	70	50	54	0.006
HTN (%)	60.0	60	55	74	ns
Diabetes (%)	14	11	18	21	ns
Coronary disease (%)	19	12	19	13	ns
CHF (%)	13	8	10	13	ns
Paroxysmal/persistent (%)	43/57	49/51	43/57	17/83	0.03
Right atrial fibrosis (%)	1.27 ± 0.38	4.65 ± 0.70	9.40 ± 2.16	12.66 ± 3.0	<0.001
AF recurrence	5%	25%	36%	79%	0.006
Pacemaker implant	0	11 (4.9%)	8 (10.3%)	3 (12.5%)	0.01

AF = atrial fibrillation; ns = nonsignificant; HTN = hypertension; CHF = congestive heart failure.

Predictors of Pacemaker Implantation

Twenty-two patients (6.39%) required dual chamber pacemaker implants during follow-up following ablation. Pacemakers were implanted for symptomatic bradycardia including sinus pauses (6 patients), sinus bradycardia (15 patients), and chronotropic incompetence (1 patient) according to guidelines.[1] The average time to pacemaker implant was 50 ± 40 days following catheter ablation.

Five patients demonstrated evidence of SND, with prolonged sinus node recovery time following termination of AF, before catheter ablation. The remainder of patients who required pacemaker implants did not manifest signs or symptoms of SND before catheter ablation of AF. Of these 5 patients, only 2 required pacemaker implants postablation.

The use of AV nodal blocking agents and antiarrhythmic drugs was compared between the pacemaker group and no-pacemaker group. No significant differences in the proportion of patients treated with β-blockers (47.6% vs 38.5%; P = 0.39), calcium channel blockers (18.7% vs 13.1%; P = 0.43), digoxin (9.5% vs 3.4%; P = 0.19), and antiarrhythmic agents (23.8% vs 23.6%; P = 0.98) were found between the 2 groups.

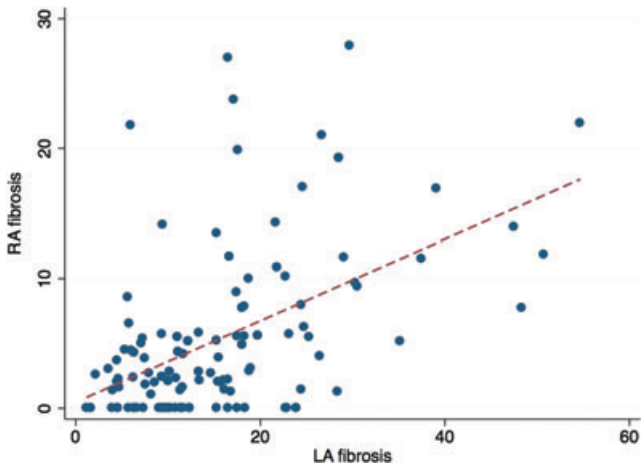

Figure 2. *Correlation between left and right atrial fibrosis—plot of left atrial fibrosis (x-axis) against right atrial fibrosis (y-axis), with a linear regression fit, illustrating that increased left atrial fibrosis is associated with a higher degree of right atrial fibrosis.*

The average LA fibrosis for patients who required pacemaker implantation was 23.4 ± 2.2% compared to 16.2 ± 0.6% for those who did not (P = 0.003). Evaluated over the stages of LA fibrosis, no patient in Utah stage 1 required a pacemaker implant, whereas 11 patients (4.5% of all stage 2 patients; average fibrosis 12.1 ± 1.3%) in Utah stage 2, 8 patients (10.2% of all stage 3 patients; average fibrosis 25.1 ± 1.1%) in Utah stage 3, and 3 patients (12.5% of all stage 4 patients; average fibrosis 42.3 ± 4.2%) in Utah stage 4 required pacemaker implants. A risk ratio for requiring a pacemaker implant of 2.93 was calculated for patients who fell into Utah stage 3 or 4 compared to patients who fell into Utah stage 2. The prevalence of persistent AF was 59.0% in the pacemaker group compared to 54.2% in the no-pacemaker group (P = 0.66).

Univariate and multivariate analysis were used to determine to the predictors of pacemaker implantation. Predictor variables included in the analysis were age, gender, type of AF, and Utah stage classification.

In univariate analysis, Utah stage (OR, 2.02; P < 0.05), patient age (OR, 1.05; P = 0.04), and female gender (OR 2.6; P = 0.04) were found to be significant predictor of pacemaker. In multivariate analysis, only Utah stage was a significant predictor of pacemaker implant with an OR of 1.88 (P < 0.05). The results of the regression analysis are summarized in Table 2.

A receiver operating characteristic (ROC) analysis was then performed to assess the predictive power of the multivariate model. The area under the curve was calculated to be 0.704, indicating that advanced stage atrial fibrosis is a strong predictor of pacemaker implantation following catheter ablation of AF (Fig. 4).

Discussion

Our study demonstrates that atrial fibrosis related to AF, detected using LGE-MRI affects the left atrium more severely than the right atrium. In addition, atrial fibrosis is shown to be a predictor of clinically significant SND requiring pacemaker implant in AF patients presenting for ablation.

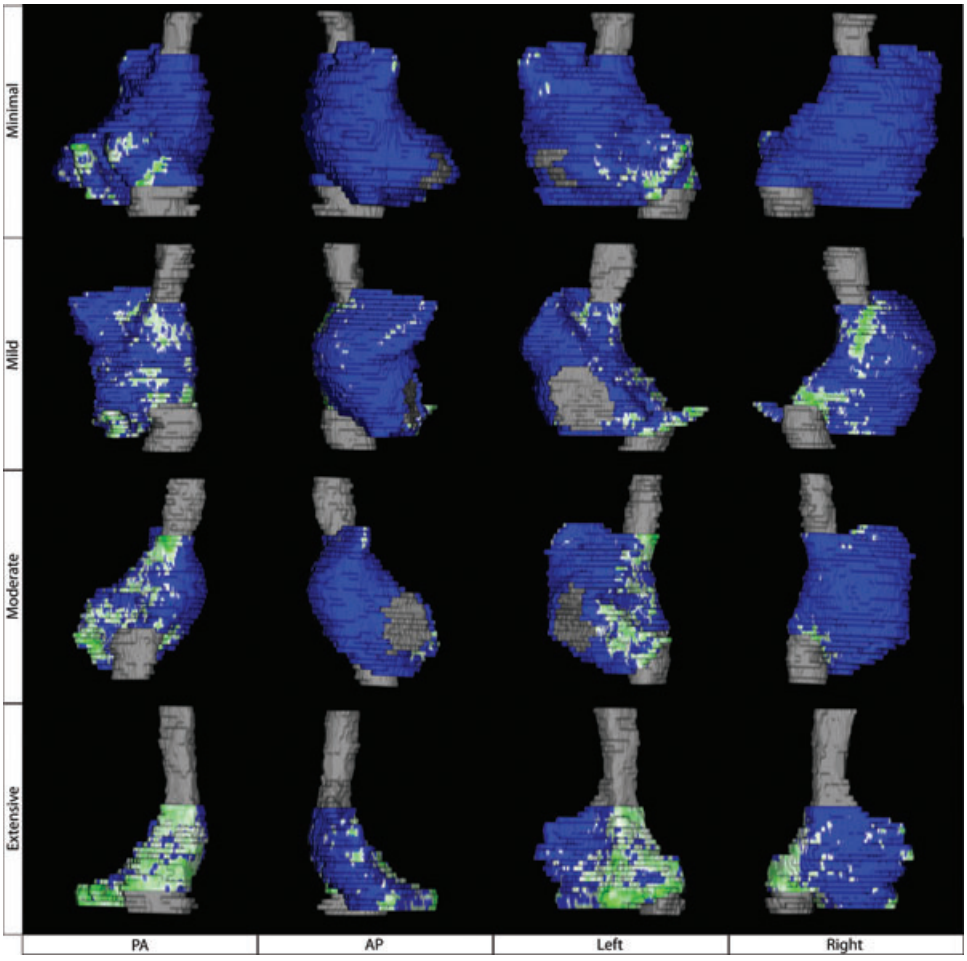

Figure 3. *Right atrial fibrosis—right atrial 3-dimensional reconstruction for 3 patients with various degrees of fibrosis. The septal region appears commonly affected at the early stage with more diffuse involvement of the right atrium at more advanced stages.*

Right Versus Left Atrial Fibrosis

AF has been demonstrated to be associated with electrical and structural tissue remodeling.[12-14] Electrical remodeling manifests with shortening and loss of rate adaptation of atrial refractoriness.[13,14] Structural tissue remodeling includes increased collagen deposition, loss of myocytes, and overall fibrosis of the atrial tissue.[12] We have previously demonstrated that the structural remodeling process can be visualized and quantified using LGE-MRI.[8] The focus of AF research and therapeutic intervention has been on the left atrium. Ablations aim to isolate AF triggers, overwhelmingly found in the pulmonary vein antral region,[15] and to modify the atrial substrate to control the arrhythmia. Our study provides quantifiable evidence that the fibrotic structural remodeling process is much less pronounced in the right atrium compared to the left atrium. The mechanism that spares the right atrium from more extensive fibrosis is not entirely clear. Using the same electrical and structural parameters, one would readily accept that the right atrium and the pulmonary circulation operate under lower filling pressures, which leads to less atrial stretch. In addition, the anatomical structure of the right atrium is obviously distinguishable from the left atrium

TABLE 2

Univariate and Multivariate Logistic Regression Analysis of Predictors of Pacemaker Implantation

	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	**Confidence Interval**	**P Value**	**Odds Ratio**	**Confidence Interval**	**P Value**
Age	1.05	0.92 – 0.99	0.04			
Male gender	0.39	0.16 – 0.96	0.04			
AF type	1.6	0.61 – 4.06	0.65			
Utah stage	2.02	1.14 – 3.56	0.015	1.88	1.05 – 3.35	0.03

AF = atrial fibrillation.

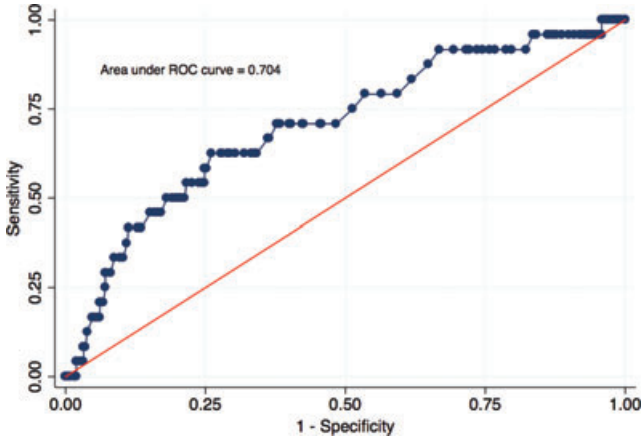

Figure 4. *ROC analysis: Received operating characteristic (ROC) curve obtained following multivariate logistic regression analysis for predictors of pacemaker implantation. The area under the curve is calculated at 0.7040 indicating that advanced atrial fibrosis is significantly associated with pacemaker implantation.*

with more extensive anterior trabeculation. Roithinger *et al.* demonstrated that patients with AF often demonstrate a more organized activation on the trabeculated right atrium.[16] The RA mass is also smaller than the left. This leaves less chance for relative refractoriness and multiple wavelets and leads to a more organized, often flutter-like activation of the right atrium. Organized atrial activity in the right atrium, in addition to the presence of anatomical barriers such as the crista terminalis and the vena cava, which serve as anatomical anchors and electrical barriers, may dampen the remodeling process in the RA chamber.

Atrial Fibrosis and Sinus Node Dysfunction

The second important finding in our study is that atrial fibrosis, quantified with LGE-MRI, is an important predictor of clinically significant SND. AF has been demonstrated to induce electrical remodeling of the sinus node both in humansand in animal models of AF.[3] Conversely, SND, with sinus bradycardia and pauses, has been shown to alter atrial refractoriness and conduction properties.[17] This bradycardia-related atrial electrical remodeling has been linked to development of AF.[18]

As with atrial electrical remodeling, sinus node function has been shown to improve following elimination of atrial tachyarrhythmias.[2,3] Hocini *et al.* demonstrated improvement in sinus pauses following catheter ablation of AF.[4] Based on their findings, one would expect some patients to have improved sinus node function following ablation. Indeed, 3 patients from our cohort, with known SND preablation, demonstrated no signs of SND during follow-up. The majority of patients who did require permanent pacemaker implantation postablation did not have manifest SND preablation. This suggests that the number of patients requiring pacemaker implants in our study is likely an underestimation of the true prevalence of SND in this AF cohort. Therefore, despite improvement in the tachycardia aspect, postablation, significant SND was still present. We believe that this is because of the fact that structural remodeling throughout the atrium, and in the sinus node region, is less reversible than electrical remodeling.

With atrial fibrosis being a key finding in patients with AF, it is not surprising to show extensive overall atrial fibrosis to be associated with significant SND. The predictive value of atrial fibrosis was evaluated with an ROC analysis demonstrating it to be a more important predictor than clinical parameters such as patient's age, gender, or the clinical AF type. This is of important clinical value with regard to managing the full spectrum of the tachycardia–bradycardia syndrome, as some patients may require pacing even after the AF has been eliminated.

Limitations

This is an observational study of patients presenting for AF ablation. The ablation procedure and subsequent scarring and inflammation may have played a role in exacerbating SND. However, all ablations were in the left atrium and the cavotricuspid isthmus region and no SVC isolations were performed, making it unlikely for ablation-related scarring to affect the sinus node region.

Not all patients who underwent LGE-MRI had quantifiable RA fibrosis. In addition, the current LGE-MRI technology does not distinguish nodal tissue from the surrounding atrial tissue. Therefore, the extent of fibrosis involving the sinus node could not be directly visualized.

Another limitation is that the decision to place a permanent pacemaker was driven by clinically manifest sinus node disease. Occult sinus node disease may have been uncovered if electrophysiology testing such as sinus node recovery time and sinoatrial conduction time would have been undertaken.

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