The degree of left atrial structural remodeling impacts left ventricular ejection fraction in patients with atrial fibrillation

Atriyum fibrilasyonlu hastalarda sol atriyumun yeniden yapılanma derecesi sol ventrikül ejeksiyon fraksiyonunu etkilemektedir

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ABSTRACT

Objectives: The extent of left atrial (LA) wall structural remodeling (fibrosis) detected by late gadolinium enhancement-magnetic resonance imaging (LGE-MRI) is correlated with advanced atrial fibrillation (AF). The concomitant occurrence of AF and left ventricular (LV) dysfunction is not uncommon. We studied the effect of LA fibrosis, a confounder of both AF and LV dysfunction, on LV ejection fraction (EF).

Study design: For the analysis, we identified and included 384 patients from our retrospective AF database who underwent LGE-MRI and transthoracic echocardiography prior to AF ablation. Based on the degree of LA fibrosis, patients were categorized into four stages as: Utah 1 (<5% LA fibrosis), Utah 2 (5–20% fibrosis), Utah 3 (20–35% fibrosis), and Utah 4 (>35% fibrosis).

Results: The average pre-ablation LVEF was 60.5%±8.5% (n=24) in Utah stage 1 patients, 55.7%±10.3% (n=240) in Utah stage 2 patients, 51.7±11.5% (n=90) in Utah stage 3 patients, and 48.9%±11.6% (n=30) in Utah stage 4 patients (p<0.001, one-way ANOVA). The percentage of LA fibrosis was significantly negatively correlated to LVEF pre-ablation in a univariate analysis (p<0.001). In a multivariate model accounting for age, gender, AF type, and comorbidities such as diabetes and hypertension, Utah stage remained a significant predictor of pre-ablation EF (p<0.001).

Conclusion: Patients with extensive LA fibrosis appear to have depressed LV function pre-ablation, suggesting that structural remodeling in the LA may also be triggering and promoting remodeling within the ventricular myocardium.

ÖZET

Amaç: Geç gadolinyum tutulumlu manyetik rezonans görüntüleme (LGE-MRI) ile saptanan sol atriyum (SA) duvarının yeniden yapılanma (fibroz) derecesi ilerlemiş atriyum fibrilasyonu (AF) ile bağıntılıdır. AF ile sol ventrikül (SV) fonksiyon bozukluğu beraberliği nadir değildir. Bu çalışmada, hem AF hem de SV fonksiyon buzukluğunda meydana gelebilen SA fibrozunun, SV ejeksiyon fraksiyonu (EF) üzerine etkisini araştırdık.

Çalışma planı: Geriye dönük AF veritabanımızdan, AF ablasyonu öncesi LGE-MRI ve transtorasik ekokardiyografi yapılmış olan 384 hasta çalışmaya dahil edildi. SA fibrozunun miktarına göre hastalar dört evreye ayrıldı; Utah I (SA fibrozu <%5), Utah II (fibroz %5 – %20), Utah III (fibroz %20 – %35) and Utah IV (fibroz >%35).

Bulgular: Ablasyon öncesi ortalama SVEF; Utah I evre hastalarda %60.5±%8.5 (n=24), Utah II evresindekilerde %55.7±%10.3 (n=240), Utah III hastalarda %51.7±%11.5 (n=90) ve Utah IV evre hastalarda %48.9±%11.6 (n=30) bulundu (p<0.001, tekyönlü ANOVA). Tek değişkenli analizde, SA fibrozu oranı LVEF ile anlamlı şekilde negatif korelasyon gösterdi (p<0.001). Yaş, cinsiyet, AF çeşidi ve diyabet, hipertansiyon gibi komorbiditeleri içeren çok değişkenli analizde, Utah evresi, ablasyon öncesi SVEF için halen anlamlı bir öngördürücüydü (p<0.001).

Sonuç: İleri derecede SA fibrozu bulunan hastalar ablasyon öncesi daha bozuk SV fonksiyonuna sahiptirler; bu da SA içindeki yeniden yapılanmanın aynı zamanda ventrikül miyokardı içindeki yeniden yapılanmayı tetikleyici ve ilerletici olabileceğini düşündürmektedir.

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Abbreviations:

AF	Atrial fibrillation
ANOVA	Analysis of variance
CHF	Congestive heart failure
IAST	Interatrial septum thickness
LA	Left atrial
LGE	Late gadolinium enhancement
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MMPs	Matrix metalloproteinases
MRI	Magnetic resonance imaging
RAAS	Renin-angiotensin-aldosterone system
SRM	Structural remodeling
TE	Echo time
TEE	Transesophageal echocardiography
TI	Inversion time
TICM	Tachycardia-induced cardiomyopathy
TR	Repetition time
TTE	Transthoracic echocardiography

Atrial fibrillation (AF), the most common arrhythmia in clinical practice, impacts cardiac efficiency and often occurs concomitantly with other cardiovascular diseases, such as left ventricular (LV) dysfunction and congestive heart failure (CHF).[1] The underlying mechanism for the occurrence of AF is predicated upon a synergistic output of electrical, contractile and structural remodeling (SRM) of the atrium.[2] Among these, the role of SRM in promoting AF has gained significant interest in recent years.[3,4] Atrial fibrosis, the major causative factor for atrial SRM, provides a viable substrate for the development and maintenance of AF.[5,6] Fibrosis results from increased interstitial collagen deposition, which may disrupt cell-to-cell coupling and thereby alter signal conduction.[7]

Atrial fibrillation significantly exacerbates the complications that may arise from HF. It is estimated that the prevalence of AF is as high as 50% in HF patients belonging to New York Heart Association (NYHA) class IV.[8,9] Poor control of the ventricular rate (fast and irregular beats) over a long period during AF adversely impacts ventricular function by way of impaired hemodynamics and increased sympathetic activation.[10] Additionally, the cellular and extracellular mechanisms involved in perpetuation of AF may also contribute to this situation.[11,12] Although AF is a well-known cause of decreased left ventricular ejection fraction (LVEF), the role of atrial fibrosis in this relationship is still unclear.

Recently, it has been demonstrated that the extent of atrial SRM relative to the atrial wall can be noninvasively assessed using the late gadolinium enhancement-magnetic resonance imaging (LGE-MRI) procedure.[13] LGE-MRI-detected fibrosis has been shown to predict procedural outcome in patients undergoing the AF ablation procedure.[4,13] While the relationship between HF and AF is well studied, the impact of left atrial (LA) tissue fibrosis identified using LGE-MRI on LV systolic function has not been evaluated.

The purpose of this study was to evaluate the relationship between the extent of atrial fibrosis and LVEF. Furthermore, we evaluated and compared the thickness of the interatrial septum in different stages of LA fibrosis.

PATIENTS AND METHODS

This retrospective study collected data from 384 patients with AF presenting to our institution for catheter ablation between October 2007 and May 2010 under a protocol approved by the Institutional Review Board of the university. All pertinent patient information gathered for the purposes of this research study were de-identified and protected in compliance with the Health Insurance Portability and Accountability Act (HIPAA) regulations. All patients underwent LGE-MRI evaluation before ablation to assess the degree of LA tissue SRM.

Transthoracic echocardiography

All patients underwent transthoracic echocardiography (TTE) before and after ablation. Echocardiography was performed using standard views and harmonic imaging (Sequoia, Siemens; Mountain View, CA). Patients with AF had echocardiographic acquisition over two seconds' duration or for two heartbeats. LV cavity and LA dimensions were obtained from M-mode echocardiograms. In the parasternal long-axis views, LA maximum parasternal diameter, interventricular septum thickness (IVST) and LV posterior wall thickness (PWT) were measured. LA volume was measured at end-systole using the biplane area-length method. In the apical four-chamber view, we measured the LV end-diastolic and end-systolic volumes, LV stroke volume index, and LVEF calculated by Simpson's method.

MRI acquisition

All MRI studies were performed on a 1.5 or 3 Tesla clinical MR scanner (Siemens Medical Solutions; Erlangen, Germany) using phased-array receiver coils. Each scan was acquired about 15 minutes following contrast agent injection (0.1 mmol/kg, Multihance, Bracco Diagnostic Inc.; Princeton, NJ) using a three-dimensional (3D) inversion recovery, respiration navigated, ECG-gated, gradient echo pulse sequence.[14]

Typical acquisition parameters were: free-breathing using navigator gating, a transverse imaging volume with voxel size = 1.25x1.25x2.5 mm (reconstructed to 0.625x0.625x1.25 mm), and inversion time (TI)=270-320 ms. The other imaging parameters were optimized for respective field strength of the scanner to improve fibrosis visibility and simultaneously keep scan duration acceptable for patients (<15 minutes) (for scans performed on 1.5 Tesla scanner: repetition time (TR)=5.4 ms, echo time (TE)=2.3 ms, and flip angle=20°, and for scans performed on 3 Tesla scanner: TR=3.1 ms, TE=1.4 ms, and flip angle=14°). ECG gating was used to acquire a small subset of phase-encoding views during the diastolic phase of the LA 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 LA. Fat saturation was used to suppress fat signal. The TI value for the LGE-MRI scan was identified using a TI scout scan. Typical scan time for the LGE-MRI study on 1.5/3 Tesla scanner was 8-12/5-9 minutes depending on the subject's heart rate and respiration pattern.

LGE-MRI quantification of pre-ablation fibrosis/structural remodeling

Left atrial wall volumes were manually segmented by expert observers from the LGE-MRI images using the Corview image processing software (MARREK Inc.; Salt Lake City, UT).[15] Quantification of LA remodeling was obtained using the methods described previously.[13] Briefly, to delineate regions of fibrosis in pre-ablation LGE-MRI images, enhancement was defined through an intensity threshold that was determined by expert inspection. A custom transfer function allowed the operator to define gradations of enhancements, while suppressing blood and normal tissue with a transfer function. Patients were then assigned to one of four groups (Utah stages 1-4) based on the percentage of LA wall enhancement. Utah 1 (minimal) was defined as <5% LA-SRM, Utah 2 (mild) as 5% and 20%, Utah 3 (moderate) as 20% and 35%, and Utah 4 (extensive) as >35% (Fig. 1).[4]

Left atrial image analysis using MRI

Interatrial septum thickness (IAST) was assessed off-line from the standard four- chamber long-axis cine images using dedicated commercially available software (OsiriX imaging software). IAST measurements were taken both during end-systole and end-diastole.

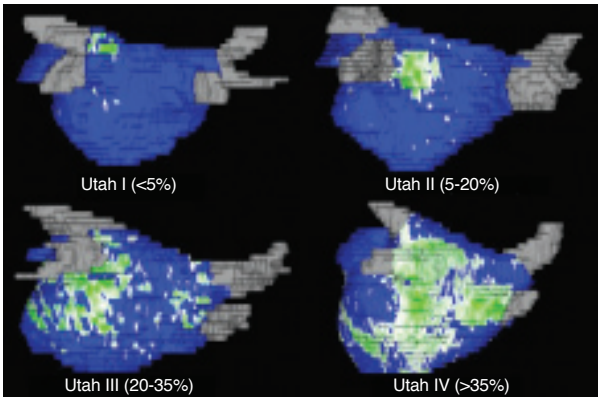

Figure 1. Staging of Utah I to IV in patients with atrial fibrillation. Posterior-anterior view of enhancement (green pattern) versus normal healthy tissue (blue) before ablation.

IAST thickness was measured at exactly 1 cm inferior to the fossa ovalis along the interatrial septum (primary atrial septum), which is considered to be the thickest part of the interatrial septum and contains a bilaminate muscle structure between endocardial surfaces.[16] We included the entire tissue as visualized using LGE-MRI to measure thickness and did not delineate fat from the myocardium.

Statistical analysis

Normal continuous variables are presented as mean ± standard deviations. Two-sample t-test and one-way analysis of variance (ANOVA) were used to test for statistical significance along with Tukey-Kramer correction for multiple comparisons. Categorical variables are presented as number and percentage of total, and statistical significance of categorical variables was assessed using Pearson's chi-square or Fisher exact tests. A multivariate logistic regression model reporting odds ratios (OR) was used to determine significant predictors of LVEF before ablation. To avoid overfitting, non-significant predictor variables were removed from the regression model in a stepwise fashion. Differences were considered significant at a p value of <0.05.

RESULTS

Pre-ablation fibrosis

Quantification of pre-ablation LA fibrosis was obtained from all 384 patients. Of the 384 patients, 24 (6.3%) were in Utah stage 1, 240 (62.5%) in Utah stage 2, 90 (23.4%) in Utah stage 3, and 30 (7.8%)

Table 1. Baseline characteristics of 384 patients presented in stages of left atrial fibrosis

	Total (n=384)		Utah 1 (n=24)		Utah 2 (n=240)		Utah 3 (n=90)		Utah 4 (n=30)		*p*
	n	%	n	%	n	%	n	%	n	%	
Age (years, Mean±SD)	65±12		64±14		64±12		67±13		70±8		**0.03**
Gender											0.14
Male	242	63.0	17	70.8	159	66.3	51	56.7	15	50.0	
Female	142	37.0	7	29.2	81	33.8	39	43.3	15	50.0	
Hypertension	238	62.0	17	70.8	145	60.4	55	61.1	21	70.0	0.60
Diabetes mellitus	66	17.2	4	16.7	33	13.8	22	24.4	7	23.3	0.10
Coronary artery disease	75	20.0	5	20.8	40	16.7	24	26.7	6	20.0	0.22
Congestive heart failure	56	14.6	2	8.3	34	14.2	14	15.6	6	20.0	0.67
Stroke	38	9.9	2	8.3	20	8.3	12	13.3	4	13.3	0.51
Valve surgery	12	3.1	0	0	6	2.5	3	3.3	3	10	0.12
Implanted device	34	8.9	1	4.2	13	5.4	14	15.6	6	20	**0.003**
Smoker	83	21.6	8	33.3	47	19.6	22	24.4	6	20	0.39
AF type											**<0.001**
Paroxysmal	178	46.4	19	79.2	116	48.3	36	40.0	7	23.3	
Persistent	206	53.6	5	20.8	124	51.7	54	60.0	23	76.7	

in Utah stage 4. Patients in the advanced LA fibrosis stages (Utah stages 3 and 4) had a higher average age, had implanted cardiac devices more often, and a higher prevalence of persistent AF. The prevalence of hypertension, diabetes, coronary artery disease, CHF, and history of stroke and smoking were comparable across patients from all four Utah stages. Patient characteristics are detailed in Table 1.

Pre-ablation left ventricular ejection fraction

The average pre-ablation LVEF was 60.5%±8.5% among patients with Utah stage 1, 55.7%±10.3% among patients with stage 2, 51.7%±11.5% among patients with stage 3, and 48.9%±11.6% among those with stage 4 ($p<0.001$, one-way ANOVA) (Fig. 2). LA fibrosis was significantly negatively correlated to LVEF pre-ablation in a univariate analysis ($R2=0.62$, $p<0.0001$). In a multivariate model accounting for age, AF type and comorbidities such as diabetes, hypertension, coronary artery disease, and mitral valve regurgitation, Utah stages remained a significant predictor of pre-ablation LVEF ($p<0.001$) (Table 2).

Patients with advanced stages of LA fibrosis had increased LA diameter and LA volume compared to those with early stages ($p=0.01$ and $p<0.001$, respec-

Table 2. Univariate and multivariate logistic regression model results

	Univariate analysis			Multivariate analysis		
	Odds ratio	Confidence interval	*p*	Odds ratio	Confidence interval	*p*
Age	1	0.98-1.01	0.78			
Atrial fibrillation type	0.35	0.24-0.50	**<0.001**	0.42	0.29-0.60	**<0.001**
Coronary artery disease	0.41	0.26-0.64	**<0.001**	0.46	0.29-0.74	**0.001**
Diabetes mellitus	0.61	0.38-0.98	**0.04**	0.63	0.39-1.05	0.53
Hypertension	1.09	0.77-1.56	0.62			
Utah Stage	0.5	0.39-0.64	**<0.001**	0.53	0.41-0.69	**<0.001**
Mitral valve regurgitation	1.76	0.85-3.62	0.12			

Table 3. Comparison of echocardiographic parameters across the four stages of atrial fibrosis

	Utah 1	Utah 2	Utah 3	Utah 4	*p*
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Left ventricular ejection fraction (%)	60.5±8.5	55.7±10.3	51.7±11.5	48.9±11.6	**<0.001**
Left ventricular end-systolic diameter	31.1±4.1	33 ±4.4	37.9±4.6	40.2±6.2	**<0.001**
Left ventricular end-diastolic diameter	46.4±5.9	46.8±6.7	51.5±6.5	52.9±8.1	**<0.01**
IVSD (mm)	11.7±3.2	10.9±1.8	11.3±2.2	11.6±1.7	**0.09**
PW (mm)	10.6±2.3	10.3±1.7	10.7±2.1	10.7±1.8	0.29
Left atrial diameter (mm)	45.2±7.5	43.7±5.5	44.2±7.8	47.6±4.4	**0.01**
Left atrial volume (ml)	63.5±15.5	72.5±26.9	85.6±28.8	106.7±35.1	**<0.001**
Mitral regurgitation grade	1.1±0.3	0.8±0.5	1.2±0.3	1.1±0.6	0.54

SD: Standart deviation; IVSD: Interventricular septal thickness in end-diastole; PW: Left ventricular posterior wall thickness in end-diastole.

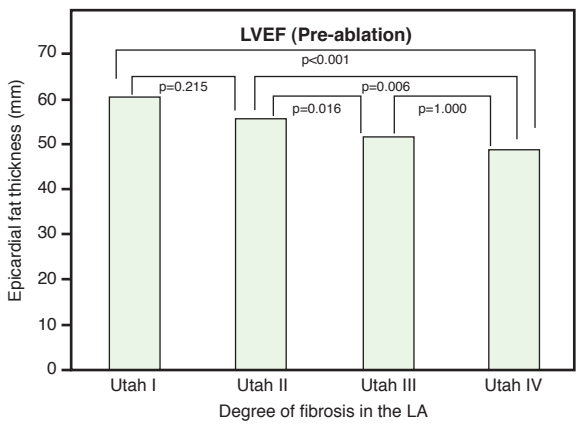

Figure 2. Pre-ablation left ventricular ejection fraction in groups Utah I to IV.

tively) (Table 3).

Correlation between atrial SRM and interatrial septum thickness

The mean IAST measured during systole of patients in the four stages were as follows: Utah 1=6.3±0.7 mm, Utah 2=6.9±1.2 mm, Utah 3=7.8±1.5 mm, and Utah 4=7.8±0.8 mm. In diastole, the mean IAST measurements were: Utah 1=5.2±0.7 mm, Utah 2=5.6±1.0 mm, Utah 3=6.2±1.2 mm, and Utah 4=6.4±0.6 mm (Fig. 3). A linear regression showed a significant correlation between LA fibrosis and both systolic IAST ($p<0.0001$) and diastolic ($p<0.0001$) IAST. Interestingly, patients in moderate/extensive groups (Utah 3/4) had a significantly thicker systolic and diastolic IAST than patients in Utah 1/2 groups ($p<0.001$).

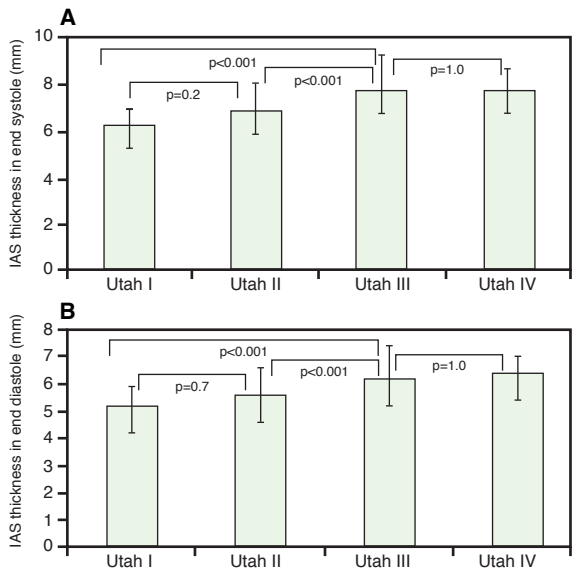

Figure 3. (A, B) Interatrial septal thickness measurements performed during systole and diastole in across the 4 stages of fibrosis.

DISCUSSION

In this study, we tested the hypothesis that increase in LA fibrosis would result in a decrease in LVEF. We found that this was in fact true. AF patients with extensive LA fibrosis appear to have significantly reduced LV function. We also identified that patients with ≥20% fibrosis in the LA had a significantly thicker interatrial septum in systole and diastole.

Atrial fibrosis and left ventricular ejection fraction

Left atrial fibrosis has been implicated as a substrate

for AF in several studies; however, the precise mechanism that explains manifestation of atrial fibrosis remains largely unknown.[17] We have previously demonstrated that the SRM process can be visualized and quantified using LGE-MRI.[13] Our study provides quantifiable evidence that the fibrotic SRM process (fibrosis) in LA is correlated to the LV systolic function in patients with AF. This atrial fibrosis has a unique way of interacting and impairing LV systolic function through several mechanisms:

1. Generalized fibrosis: Several studies have also demonstrated the presence of fibrosis in the ventricle in patients with AF.[5,18] We speculate that fibrosis is a diffuse disease affecting both atria and ventricles, although the former is more susceptible than the latter. This may be because the atrial fibroblast proliferation in response to growth factors (especially platelet-derived growth factors) and the proportion of fibroblast volume are greater in the atrium than in the ventricles.[19] Poorly controlled ventricular rate, which is a common clinical scenario in AF patients, also contributes to the development of ventricular fibrosis.[20] We think that, in patients with advanced-degree atrial fibrosis, ventricles are more involved in the fibrotic process than in patients with early-degree fibrosis. AF and ventricular fibrosis together will cause a composite decrease in LVEF in this group of patients.

2. Tachycardia-induced cardiomyopathy (TICM): Previous studies have reported that TICM could account for up to 40%-50% of AF-associated LV dysfunction.[21,22] It has been demonstrated that rapid pacing results in reduction in ventricular function, and cessation of pacing results in improvement in LVEF.[12,23] Rapid ventricular response reduces ventricular function via cellular and extracellular remodeling, which causes myocyte malalignment and myocyte loss that finally culminates with contractile dysfunction.[23,24] On the other hand, tachycardia can also simultaneously induce atrial SRM and atrial fibrosis, thus playing role in both induction and perpetuation of AF.[25] Thus, a vicious cycle ensues: atrial fibrosis causes AF, AF leads to tachycardia, tachycardia causes LV dysfunction, and LV dysfunction in turn leads to atrial fibrosis.

Another mechanism that inter-relates TICM to fibrosis is the mechanosensitive channels. Clemo et al.[26] reported the presence of these channels in fibroblasts and their interactions with cardiomyocytes, and showed that the stretching of fibroblasts during atrial diastole could increase the spontaneous depolarization rate of pacemaker cells. This stretch-responsive activation of fibroblasts can potentially trigger a faster heart rate that can contribute to the development of cardiomyopathy. On the other hand, increase in the degree of fibrosis correlates with the increase in the number of fibroblasts, thus indirectly corresponding to the initiation of stretch-induced cardiomyopathy. This explanation could be another plausible scenario leading to the reduced LVEF prior to ablation in patients with extensive atrial fibrosis observed in our study.

Since the degree of dysfunction correlates with the duration of the tachycardia, it is reasonable to think that TICM occurs more commonly in patients with persistent AF than in paroxysmal AF patients. In the present study, Utah stage 1 and 2 patients had paroxysmal AF more often, whereas the majority of patients in Utah stages 3 and 4 suffered from persistent AF, demonstrating that TICM may be the cause of decreased EF in patients with extensive LA fibrosis.

3. Atrial enlargement and matrix metalloproteinases: Atrial stretch increases gene expression via stretch-activated channels and leads to cellular hypertrophy, degeneration and interstitial fibrosis.[27] In dilated atria, enlarged myocytes are an important source for collagenases like matrix metalloproteinases (MMPs), which play an important role in extracellular matrix homeostasis in the atrial myocardium during HF.[28] The progression of LV dysfunction has been shown to be significantly associated with increased MMP activity, specifically MMP-2 and MMP-7, which are active components of atrial fibrosis.[3] Although we did not measure the plasma concentrations of MMP, the significantly larger LA size in patients with advanced stages of fibrosis can be taken as an indicator of greater MMP activity, which in turn explains the greater LA-SRM in this cohort of patients.

4. The role of the renin-angiotensin-aldosterone system: Patients with AF have increased activation of the renin-angiotensin-aldosterone system (RAAS).[29] The RAAS has been noted to play a role in AF, and various studies have demonstrated the beneficial effect of angiotensin-converting enzyme inhibition on AF.[29,30] This neurohormonal system axis, angiotensin II and aldosterone in particular, is known to provoke myocardial fibrosis.[31] We think that this pro-

cess of fibrosis occurs simultaneously in the atrium as well as the ventricle, but is likely to be faster in the atrium since the damage is more pronounced and more rapid in the atrium compared to the ventricle. The development of ventricular fibrosis leads to a decrease in LVEF, causing the onset of another vicious cycle: decreased EF leading to increase in atrial fibrosis by increasing the RAA system, causing increased myocyte stretch and LA pressure, which in turn leads to more atrial fibrosis.[29]

Presence of coronary artery disease was also found to be a significant predictor of LVEF in our study. This is not unexpected since ischemic heart disease is well known to be an initiator and contributor to the progression of LV dysfunction. Loss of functioning myocytes after myocardial infarction or hibernating and stunned myocardium in chronic ischemia may result in a decline in LV function.

Atrial fibrosis and interatrial septum thickness

Atrial septum thickness has been shown to be correlated with aging, obesity and coronary artery disease.[32,33] López-Candales et al.[34] showed that IAST increased in patients with AF compared to patients without AF; however, they did not find any correlation between the degree of IAST and the duration of AF. In the above-mentioned studies, IAST was measured using transthoracic (TTE) or transesophageal (TEE) echocardiography. In the current study, we measured IAST using MRI, which delineates cardiac structures better than TTE or TEE.[35] To our best knowledge, we are the first to demonstrate the correlation between degree of atrial fibrosis and increased IAST. We found that patients with extensive LA fibrosis (≥20% fibrosis in the LA) had a significantly thicker IAS in both systole and diastole. Based on our results, we speculate that the atrial septum is spared in the early stages of atrial SRM; however, it is more pronounced in advanced stages of atrial SRM. This might have three important clinical implications. First, if atrial septal hypertrophy occurs alongside progression of SRM in the LA, it could serve as a marker to monitor the progression of AF. Second, the atrial septum could be a potential target for ablationists in patients with extensive LA fibrosis. Third, patients with greater SRM in the atrium may require longer durations or higher wattage of radiofrequency energy delivered during the ablation procedure in order to realize transmural lesions.

Limitations

The number of patients in the different Utah stages is unbalanced (especially for Utah stages 1 and 4). A more balanced sample size across the different stages would potentially allow for a better comparison between these groups. In addition, the MRI operator selection of an incorrect inversion time, the presence of respiratory navigator artifacts, and other MRI noise may lead to the inappropriate detection and quantification of fibrosis; in spite of this, such effects seemed to be minimal in this study because all included LGE-MRIs could be analyzed for segmentation and quantification. The estimation of interatrial septum size may vary due to shape of the atrial septum and resolution of the MR image. Additionally, disorders that may lead to thicker atrial septum, such as infiltrative diseases and cysts, were not excluded from our study, which may potentially bias the results of this study.

In conclusion, the present study indicates that patients with extensive atrial fibrosis have a lower EF, suggesting that SRM in the LA may also be triggering and promoting remodeling within the ventricular myocardium. On the other hand, patients with extensive atrial fibrosis were found to have a thicker interatrial septum, suggesting that atrial septal hypertrophy may occur along with the progression of SRM within the LA. Hence, IAST could serve as a surrogate marker to monitor the progression of AF.

Conflict-of-interest issues regarding the authorship or article: None declared

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