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Exercise Capacity Correlates With Left Atrial Structural Remodeling as Detected by Late Gadolinium-Enhanced Cardiac Magnetic Resonance in Patients With Atrial Fibrillation

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ABSTRACT

OBJECTIVES This study hypothesized that left atrial structural remodeling (LA-TR) correlates with exercise capacity (EC) in a cohort of patients with atrial fibrillation (AF).

BACKGROUND Late gadolinium-enhanced cardiac magnetic resonance (LGE-CMR) imaging provides a method of assessing LA-TR in patients with AF.

METHODS A total of 145 patients (32% female, mean age 63.4 $\pm$ 11.6 years of age) with AF (66 paroxysmal, 71 persistent, 8 long-standing persistent) presenting for catheter ablation were included in the study. All patients underwent LGE-CMR imaging as well as maximal exercise test using the Bruce protocol prior to catheter ablation of AF. EC was quantified by minutes of exercise and metabolic equivalent (MET) level achieved. LA-TR was quantified from LGE-CMR imaging and classified according to the Utah classification of LA structural remodeling (Utah stage I: $<$10% LA wall enhancement; Utah II: 10% to $<$20%; Utah III: 20% to $<$30%; and Utah IV: $>$30%). AF recurrence was assessed at 1 year from the date of ablation.

RESULTS The average duration of exercise was 8 $\pm$ 3 min, and the mean MET achieved was 9.7 $\pm$ 3.2. METs achieved were inversely correlated with LA-TR ($R^2 = 0.061$; $p = 0.003$). The duration of exercise was also inversely correlated with LA-TR ($R^2 = 0.071$; $p = 0.001$). Both EC and LA-TR were associated with AF recurrence post ablation in univariate analysis, but only LA-TR and age were independently predictive of recurrence in multivariate analysis ($p = 0.001$). For every additional minute on the treadmill, subjects were 13% more likely to be free of AF 1 year post ablation ($p = 0.047$).

CONCLUSIONS EC is inversely associated with LA-TR in patients with AF and is predictive of freedom from AF post-ablation. (J Am Coll Cardiol EP 2016;2:711-9) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drug

AF = atrial fibrillation

BB = beta-blocker

CAD = coronary artery disease

CCB = calcium-channel blocker

CHF = congestive heart failure

DM = diabetes mellitus

EC = exercise capacity

LA = left atrium

LA-TR = left atrial structural remodeling

LGE-CMR = late gadolinium-enhanced cardiac magnetic resonance

LV = left ventricle

LVEF = left ventricular ejection fraction

MET = metabolic equivalent

PV = pulmonary vein

Exercise capacity (EC), a robust predictor of cardiovascular outcomes, is associated with cardiac morbidity and mortality (1). The relationship between atrial fibrillation (AF) and EC is complex and often related to left ventricular (LV) function. However, even in patients with preserved LV function, AF is associated with diminished EC. Successful cardioversion or catheter ablation can improve EC by restoring normal sinus rhythm (2–5).

Abundant evidence has linked left atrial structural remodeling (LA-TR) with the pathophysiology of AF (4). The severity of AF's impact on a patient's EC may be dictated in part by the extent of LA-TR (6). Patients with AF have decreased regional LA function, manifested as lower strain and strain rate (7), and are more likely to have LA enlargement (8,9). Catheter ablation, conversely, has been shown to result in improved LA function with the restoration of sinus rhythm (10). Moreover, regression of dilated chambers can be achieved with sinus rhythm (11).

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Late gadolinium-enhanced cardiac magnetic resonance (LGE-CMR) imaging can be used for assessment and quantification of LA-TR (12). LA-TR by LGE-CMR imaging has been shown to strongly predict the success of and aid in patient selection for AF ablation (13). LA-TR is also inversely related to echocardiographically determined LA strain and strain rate (14). As LA-TR progresses, LA active transport function decreases. This decrease in LA transport has been closely associated with functional capacity, although the strength of this relationship remains unclear (2,15).

We hypothesized that there is an inverse relationship between the extent of LA-TR and EC determined by a maximal treadmill test. We also hypothesized that patients with greater baseline EC were more likely to achieve freedom from AF after catheter ablation.

METHODS

We conducted a retrospective review of patients who presented to the University of Utah for treatment of AF between December 2006 and October 2010. The database study protocol was reviewed and approved by the University of Utah Institutional Review Board and was HIPAA compliant. The two inclusion criteria for this study were patients with AF and LGE-CMR evaluation to assess the extent of LA-TR, a maximal exercise treadmill test using the Bruce protocol (16). All patients were asymptomatic at rest. A total of 145 patients met the inclusion criteria and were included in the analysis. Recurrence rates were assessed at 1 year (365 days), including a blanking period of 90 days.

CMR IMAGE ACQUISITION. All LGE-CMR scans were obtained using either a 1.5-T Avanto or a 3-T Verio clinical scanner (Siemens Medical Solutions, Erlangen, Germany), using a total imaging matrix phased-array receiver coil. Each scan was acquired approximately 15 min after contrast agent injection (0.1 mmol/kg Multihance [Bracco Diagnostic Inc., Princeton, New Jersey]), using a 3-dimensional (3D) inversion recovery, respiration-navigated, electrocardiographically (ECG)-triggered gradient echo pulse sequence. Inversion preparation was applied every heartbeat, and fat saturation was applied immediately before data acquisition. Data acquisition was limited to 15% of cardiac cycle and was performed during LA diastole. The time interval between the R peak of the ECG and the start of data acquisition was defined by using cine images of the LA. Typical acquisition parameters were free-breathing using navigator gating, a transverse imaging volume with a voxel size of $1.25 \times 1.25 \times 2.5$ mm (reconstructed to $0.625 \times 0.625 \times 1.25$ mm), and inversion time (TI) of 270 to 310 ms. The other scan parameters for 3D LGE of LA at 3-T were: repetition time (TR) = 3.1 ms, echo delay time (TE) = 1.4 ms, and a flip angle = 14°. Scan parameters for 3D LGE of LA using the 1.5-T machine were TR/TE = 5.2/2.4 ms and a flip angle = 20°. The TE for the scans 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 LA wall boundary. The TI value for the LGE-CMR scan was identified using a TI scout scan acquired in short-axis view of the left ventricle. TI was selected based on nulling of LV myocardium. Typical scan time for LGE study was 7 to 12 min at 1.5-T or 5 to 9 min at 3-T, depending on patient respiration.

LGE-CMR QUANTIFICATION OF LA-TR. LA wall volumes were manually segmented by expert observers from the LGE-CMR images, using Corview image processing software (Marrek Inc., Salt Lake City, Utah). The protocol for segmentation proceeded as follows. First, the endocardial border of the LA was defined, including an extent of pulmonary vein (PV) sleeves, by manually tracing the LA-PV blood pool in each slice of the LGE-CMR volume. Next, the endocardial segmentation was morphologically dilated and then manually adjusted to create an assessment of the boundary of the epicardial LA surface. Finally, the endocardial segmentation was subtracted from the epicardial segmentation to define a wall segmentation, which was manually edited to exclude the mitral valve and PVs. Thus, the resulting LA wall segmentation included the 3D extent of both the LA wall and the antral regions of the PVs.

Quantification of LA remodeling was obtained using methods previously described (12–14). Briefly, to delineate regions of fibrosis in pre-ablation LGE-CMR images, we defined enhancement through an intensity threshold that was determined by expert inspection. To assist this process, initial visualization used a volume-rendering tool in Corview software that allowed the operator to visualize the distribution of enhancement in 3D. A customized 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 1 of 4 groups (Utah stages I to IV) based on the percentage of LA wall enhancement. Utah I was defined as <10% LA-TR; Utah II as ≥10% and <20%; Utah III as ≥20% and <30%; and Utah IV as ≥30%.

ABLATION PROCEDURE. Details of the ablation procedures, namely PV isolation as well as posterior wall and septal debulking, have been described previously (17,18). Briefly, the catheters were guided into the LA through 2 trans-septal punctures under intracardiac echo guidance, using a phased-array catheter (AccuNav, Siemens Medical Solutions USA, Inc., Mountain View, California). Specifically, a 10-pole circular mapping catheter (Lasso, Biosense Webster Inc., Diamond Bar, California) and a 3.5-mm-diameter Thermocool ablation catheter (Biosense Webster Inc.) were advanced into the LA for mapping and ablation. A 14-pole catheter (TZMedical, Portland, Oregon, or Bard EP, Lowell, Massachusetts) was used to record right atrial and coronary sinus electrograms and also as the reference catheter for 3-D electroanatomical mapping with CARTO (Biosense Webster Inc.). Radiofrequency energy was delivered with 50 W at a catheter tip temperature of 50°C for no longer than 5 s; procedural endpoints were guided by electrogram abolition, as recorded with the lasso catheter. Ablation lesions were placed in a circular fashion in the PV antral region until electrical isolation of the PVs was achieved. Additional lesions were placed along the LA posterior wall and septum (17). At the end of all procedures, 15 μg/min of isoproterenol, in addition to burst atrial pacing at 200 ms, was performed to rule out initiation of AF or atrial flutter.

FOLLOW-UP AND RECURRENCE. A post-ablation 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 or antiarrhythmic drugs (AADs), or both; AADs (when used) 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 underwent 12-lead ECG and an 8-day Holter monitor for detection of arrhythmia recurrence post blanking. 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 s without AAD treatment following the 3-month blanking period, as suggested by the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society expert consensus statement (19). All ablation procedures were performed using therapeutic anticoagulation with warfarin. Warfarin therapy was continued post procedure to maintain an international therapeutic ratio of 2.0 to 3.0.

EXERCISE TESTING. Treadmill exercise testing was performed using the Bruce protocol. All treadmill tests were performed within 227 ± 426 days of the LGE-CMR scan. Heart rate and blood pressure were recorded every 2 min throughout the test. Metabolic equivalents (METs) were estimated from peak exercise speed and grade using standardized equations (20). Study subjects were encouraged to provide a maximal effort; no heart rate targets were used to terminate the test. However, standard clinical indications for stopping the test were used. EC was measured in maximal METs level achieved on the treadmill as well as maximal duration of exercise (in minutes). Additionally, medication lists were obtained at the time of treadmill testing and/or follow-up visits.

ECHOCARDIOGRAPHY. Patients also received 2-dimensional echocardiograms with left ventricular ejection fraction (LVEF) measurements as part of usual care. Baseline LVEF was recorded in 133 patients who underwent LGE-CMR. Additionally, follow-up (post-ablation) EF data were obtained in 117 patients.

STATISTICAL ANALYSIS. Continuous variables are mean ± SD, and dichotomous data are proportions and percentages. Continuous variable means were compared using one-way analysis of variance (ANOVA), and categorical variables were compared using chi-square tests. For primary analyses, a series of pairwise comparisons were made among Utah Stages of fibrosis, using Utah Stage I as a common reference group, and the Holm procedure was used to control for multiple comparisons (21). Linear regression analysis was used to examine the relationship between the degree of LA-TR and EC

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TABLE 1 Baseline Characteristics by Utah Stage

	Utah Stage 1 (n = 49)	Utah Stage 2 (n = 60)	Utah Stage 3 (n = 24)	Utah Stage 4 (n = 12)	p Value*
Age, yrs	61 ± 12	64 ± 11	64 ± 12	68 ± 11	0.372
Males	37 (76)	42 (70)	15 (63)	5 (42)	0.135
BMI, kg/m^2	28 ± 6	29 ± 5	30 ± 8	29 ± 5	0.668
LVEF, %	60 ± 8	58 ± 8	59 ± 6	60 ± 3	0.813
LA volume, ml	86 ± 35	96 ± 36	109 ± 60	128 ± 56	**0.011**
HTN	32 (65)	31 (52)	13 (54)	9 (75)	0.305
Diabetes	4 (8)	5 (8)	3 (13)	3 (25)	0.332
Coronary disease	6 (12)	7 (12)	7 (29)	3 (25)	0.157
CHF	4 (8)	2 (3)	0 (0)	2 (17)	0.140
AF type					
Paroxysmal	24 (49)	29 (48)	10 (42)	3 (25)	
Persistent	22 (45)	29 (48)	11 (46)	9 (75)	0.356
Chronic	3 (6)	2 (3)	3 (13)	0 (0)	
Beta-blockers	16 (33)	14 (24)	7 (29)	6 (50)	0.324
Calcium channel blockers	9 (19)	12 (21)	5 (21)	2 (17)	0.988
Digoxin	4 (9)	7 (12)	2 (8)	3 (25)	0.416
Antiarrhythmic drugs	5 (11)	9 (16)	7 (29)	1 (8)	0.196

Values are mean ± SD or n (%). Significant p values are in **bold**. *Model adjusted for all covariates the demonstrated a univariate association p < 0.05.

AF = atrial fibrillation; BMI = body mass index; CHF = congestive heart failure; HTN = hypertension; LA = left atrium; LVEF = left ventricle ejection fraction.

(maximal MET level achieved on the treadmill and the maximal duration of exercise measured in seconds). Univariate and multivariate Cox proportional hazard models were used to determine predictors of time until AF recurrence, including EC and LA-TR. All variables presented in **Tables 1 and 2** were evaluated for inclusion in the multivariate mode. Those variables that demonstrated univariate association ($p < 0.20$) were included in the multivariate model. As a sensitivity analysis, a second multivariate model was constructed including only those variables that demonstrated a statistically significant univariate association ($p < 0.05$). All covariates in the final model are presented in **Table 3**. A test of the proportional hazards was performed for each covariate and globally using a formal significance test based on the unscaled and scaled Schoenfeld residuals. No departures from model assumptions were observed. All statistical analyses were performed either using SAS version 9.0 or STATA/SE version 14.1 software (StataCorp, College Station, Texas).

TABLE 2 Exercise Data by Utah Stage

Exercise Data	Utah Stage 1 (n = 49)	Utah Stage 2 (n = 60)	Utah Stage 3 (n = 24)	Utah Stage 4 (n = 12)	p Value
MET level achieved	10.2 ± 3.2	9.7 ± 3.3	9.4 ± 2.7	7.3 ± 2.3	**0.035**
Exercise duration, min	8.7 ± 3.1	8.0 ± 3.1	7.7 ± 2.5	5.6 ± 2.5	**0.017**
Baseline HR	68 ± 15	71 ± 16	71 ± 16	79 ± 21	0.306
Baseline SBP	127 ± 21	129 ± 17	136 ± 19	134 ± 18	0.232
Maximum HR	156 ± 28	154 ± 21	153 ± 27	148 ± 30	0.774
Maximum SBP	159 ± 27	157 ± 28	161 ± 33	159 ± 32	0.969
Maximum rate-pressure product	24556 ± 6303	24471 ± 5889	24978 ± 6059	23939 ± 7940	0.974
Inducible ischemia on ETT (%)	3 (6)	2 (4)	1 (4)	1 (9)	0.832
AF during ETT (% patients)	12 (25)	20 (34)	7 (29)	4 (36)	0.725

Values are mean ± SD or n (%). Significant p values are in **bold**.

AF = atrial fibrillation; ETT = exercise treadmill test; HR = heart rate; MET = metabolic equivalent; SBP = systolic blood pressure.

RESULTS

BASELINE CHARACTERISTICS. A total of 145 patients with LGE-CMR scans and completely documented treadmill tests were included in our analysis. The average age of our cohort was 63.4 ± 11.6 years. A minority of subjects were female (n = 46 [32%]). Sixty-six of 145 patients (46%) had paroxysmal AF, whereas 71 patients (49%) had persistent AF, and 8 patients (6%) had long-standing persistent AF. The mean LVEF of our cohort was normal (59 ± 7%), and greater than one-half of the patients (59%) were hypertensive. A minority of patients had a history of smoking (23%), coronary artery disease (CAD) (16%), diabetes mellitus (DM; 10%), history of stroke (11%), history of coronary artery bypass graft (4%), and congestive heart failure (CHF; 6%). The majority of patients (69%) had $CHADS_2$ scores (where $CHADS_2$ stands for congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, TIA, or thromboembolism) of 0 or 1. The average body mass index of all included patients was 28.9 ± 5.7 kg/m^2. Medication histories were also obtained. Thirty percent of patients were taking beta-blocker (BB) medication, of which metoprolol was the most common. Nineteen percent of patients were taking a calcium-channel blocker (CCB), 16% were receiving an AAD (11 were on flecainide or propafenone, 9 were on sotalol or dofetilide, 1 was on amiodarone, and 1 was on quinidine therapy), and 11% were taking digoxin.

PRE-ABLATION LEFT ATRIAL DELAYED ENHANCEMENT. Average pre-ablation LA-TR was 16.1 ± 10.0% (n = 145) of the LA wall volume. In total, 49 patients (33.8%) were classified as Utah I, 60 (41.4%) as Utah II, 24 (16.6%) as Utah III, and 12 (8.3%) as Utah IV. Ages at the time of CMR image acquisition, prevalence of hypertension (HTN), CAD, CHF, DM, and LVEF were comparable across the 4 stages. LA volume was higher in advanced Utah stages. Medication usage was not significantly different across patients in the 4 stages. Details of subjects' baseline

TABLE 3 Univariate and Multivariate Cox Proportional Hazards Models for Time to AF Recurrence After Catheter Ablation

	Univariate		Multivariate			
			Model 1		Model 2	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
LA-TR, per 10%	1.60 (1.25–2.06)	**<0.001**	1.51 (1.09–2.09)	**0.014**	1.48 (1.11–1.98)	**0.008**
METs, per 1 U	0.88 (0.78–0.99)	**0.027**	0.84 (0.36–1.96)	0.689	0.64 (0.32–1.27)	0.200
Age, per 10 yrs	1.90 (1.27–2.84)	**0.002**	1.43 (0.85–2.41)	0.179	1.39 (0.87–2.23)	0.172
Males	0.78 (0.39–1.58)	0.493				
BMI, per 1 kg/m^2	1.01 (0.95–1.06)	0.782				
LVEF, per 10%	1.47 (0.76–2.83)	0.255				
LA volume, per 10 ml	1.07 (1.00–1.15)	0.065	1.01 (0.99–1.02)	0.344		
CHF	1.27 (0.303–5.28)	0.747				
CAD	1.14 (0.47–2.75)	0.774				
HTN	2.32 (1.05–5.13)	**0.037**	1.59 (0.63–4.05)	0.331	1.54 (0.66–3.60)	0.320
DM	2.13 (0.93–4.89)	0.075	2.61 (0.87–7.81)	0.087		
Stroke	1.34 (0.83–2.15)	0.232				
Persistent or chronic AF (reference = paroxysmal)	2.32 (1.11–4.85)	**0.026**	1.06 (0.41–2.78)	0.902	1.41 (0.61–3.25)	0.424
BB	0.68 (0.35–1.51)	0.347				
CCB	1.80 (0.84–3.86)	0.130	1.15 (0.44–3.02)	0.770		
AAD	1.70 (0.77–3.78)	0.190	1.90 (0.72–5.02)	0.197		
Digoxin	1.63 (0.63–4.20)	0.316				
Exercise duration, per 1 min	0.89 (0.79–1.00)	**0.043**	1.25 (0.52–3.01)	0.621	1.63 (0.81–3.26)	0.172
Baseline HR, per 10 beats/min	1.03 (0.83–1.28)	0.772				
Maximum HR, per 10 beats/min	0.85 (0.73–0.98)	**0.028**	0.95 (0.80–1.14)	0.586	0.90 (0.77–1.06)	0.211
Baseline systolic BP, per 10 mm Hg	1.01 (0.84–1.22)	0.900				
Maximum systolic BP, per 10 mm Hg	0.91 (0.80–1.04)	0.181	0.90 (0.76–1.06)	0.203		
Ischemia on ETT	0.60 (0.08–4.39)	0.614				
AF during ETT	0.71 (0.31–1.64)	0.422				

Significant p values are in **bold**.

AAD = antiarrhythmic drug; BB = beta-blocker; BP = blood pressure; CAD = coronary artery disease; DM = diabetes mellitus; HR = hazard ratio; LA-TR = left atrial structural remodeling; other abbreviations as in Tables 1 and 2.

characteristics and exercise data divided by LA-TR stage are shown in Tables 1 and 2, respectively.

EC AND LA REMODELING. Correlation of maximal EC on treadmill testing and LA-TR, modeled as a continuous variable, was studied using linear regression. In univariate analysis, we found that the higher the METs achieved during exercise, the lower the degree of LA-TR quantified from LGE-CMR imaging ($R^2 = 0.061$; $p = 0.003$) (Figure 1). This value remained significant after adjusting for baseline rhythm (sinus vs. AF), AF type (paroxysmal vs. persistent/chronic), and body mass index (BMI). There was also a significant association between degree of LA-TR and EC measured by duration of exercise (in minutes on the treadmill; $R^2 = 0.071$; $p = 0.001$).

There were significant differences in EC (METs) across the Utah stages of fibrosis ($p = 0.035$) (Figure 2). Compared to Utah Stage I, only Utah Stage IV remained significant when adjusting for multiple comparisons ($p = 0.011$).

In multivariate linear regression analysis, LA-TR remained significantly correlated with EC (measured in minutes on the treadmill) when adjusting for age and comorbidities (CHF, HTN, DM, CAD, and history of stroke; $p = 0.022$). When medications (BB, CCB, and AAD) are added to the model, LA-TR still remained significantly associated with EC ($p = 0.008$.) Additionally, the association remained significant when baseline rhythm, occurrence of any AF on the treadmill, or both were added to the model ($p = 0.014$).

EC AND RHYTHM AT TIME OF TREADMILL TESTING. Although all patients in the study had diagnoses of AF, only 43 patients (30%) were in atrial fibrillation at the time of treadmill testing. AF was present at the time of treadmill testing in 24% Utah Stage I patients, 34% of Utah II, 25% of Utah III, and 42% of Utah IV. There was no significant association between the rhythm at the time of exercise testing and Utah stage ($p = 0.531$).

Patients in sinus rhythm at the time of exercise testing had a lower baseline heart rate (66 vs. 82 beats/min), lower maximum heart rate (149 vs. 167 beats/min), and greater EC (10.4 METs vs. 7.6 METs) than patients in AF during treadmill testing ($p < 0.001$ for all comparisons) (Figure 3). The mean number

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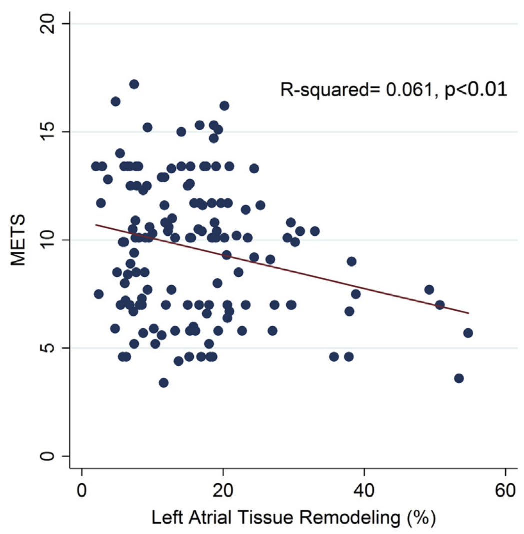
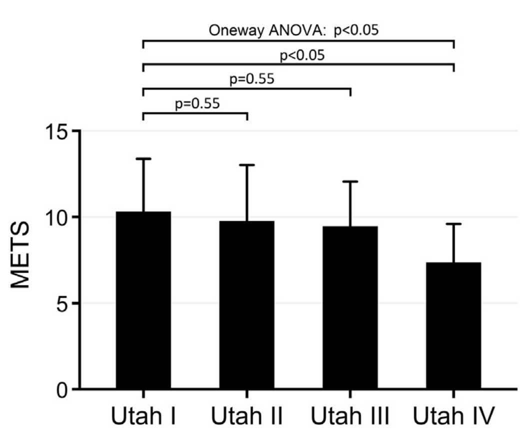
FIGURE 1 **LA Tissue Remodeling**



LA tissue remodeling (% of LA wall volume) on the x-axis, and MET level achieved on the y-axis. A best-fit line is shown. $R^2 = 0.061$; $p = 0.003$. LA = left atrium; MET = metabolic equivalent.

of MET achieved for subjects with paroxysmal AF was 10.9 MET, 8.6 MET for persistent, and 8.1 MET for long-standing persistent ($p < 0.001$). All associations remained significant when adjusting for baseline medications (BB, CCB, AAD, and digoxin). There were no statistically significant interactions between high (Utah III or IV) or low (Utah I or II) LA-TR and baseline rhythm, whereby the degree of LA-TR modified the effect of rhythm on baseline HR

FIGURE 2 **Box Plot Shows METs on the Y-Axis and Utah Stage of Atrial Fibrosis on the X-Axis**



Significant pair-wise mean comparisons are noted. MET = metabolic equivalent.

($p = 0.135$), maximum HR ($p = 0.772$), or MET achieved ($p = 0.083$).

AF RECURRENCE. Of the 145 patients enrolled in this study, 122 patients underwent a single ablation procedure and had recurrence data recorded 1 year from the procedure. Of these patients, the average duration of exercise was 8.2 ± 2.9 min, which corresponded to a mean achieved MET level of 9.8 ± 3.0. The mean MET level achieved for patients without recurrence of AF after ablation was 10.2 ± 3.1 MET compared to 8.9 ± 2.8 MET for those with AF recurrence ($p = 0.026$) (Figure 4). For every additional 1-minute on a Bruce protocol, patients undergoing AF ablation had a 13% greater likelihood of freedom from AF post ablation ($p = 0.047$).

In univariate Cox proportional hazards regression analysis for time to recurrence, LA-TR, METs achieved on a treadmill, age, LA volume HTN, diabetes, AF type, CCB, AAD, duration of exercise, max heart rate, and max systolic BP all demonstrated some association with the likelihood of recurrence post AF ablation ($p < 0.20$). In multivariate analysis, however, only the percent of LA-TR remained significantly associated with the outcome from AF ablation at a p value of < 0.05 (Table 3).

BASELINE EC AND THE OUTCOME FROM AF ABLATION. In an effort to explore the relationship between baseline EC and the outcome of AF ablation, we took all patients with exercise data and divided them into quartiles of EC (as measured by minutes on the treadmill). Quartile 4 was denoted the “Highest Fitness” category, and quartiles 1 to 3 were denoted “lower fitness” quartiles. Mean exercise duration in the highest fitness category versus the lower fitness categories was 11.8 min versus 4.3 min. Kaplan-Meier analysis was then performed for time to AF recurrence post ablation stratified by patients according to fitness quartiles (log-rank test; $p = 0.041$) (Figure 5).

DISCUSSION

The findings of the current study can be summarized as follows. EC correlates with the degree of LA-TR as assessed by LGE-CMR imaging. As the degree of LA-TR increases, EC decreases. Furthermore, both EC and LA-TR predict the recurrence of AF after ablation; however, only LA-TR and age is independently associated with AF recurrence when adjusted for co-morbidities. This suggests that, while LA-TR and EC are closely related, the dominant variable with respect to outcome remains LA-TR by LGE-CMR imaging. Secondary findings in our study are that the mean MET level achieved for patients with paroxysmal AF was significantly higher than for patients with persistent AF. Also, the presence of AF acutely during treadmill testing is associated with a higher baseline and max heart rate, and lower overall MET levels as compared to patients in sinus rhythm at the time of testing. These associations remained significant when we adjusted for baseline rate control and rhythm control medications.

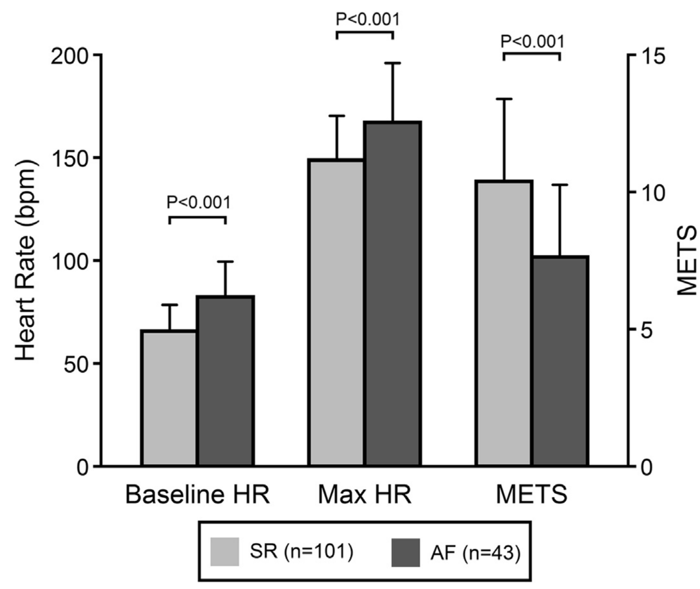
This is the first study demonstrating the association between LA-TR (as assessed using LGE-CMR imaging) and EC. It has been shown previously that AF affects EC. In a substudy of the SAFE-T (Sotalol-Amiodarone AF Efficacy Trial) involving 555 patients, Atwood et al. (2) showed that symptomatic AF was associated with a reduction in baseline EC and that successful cardioversion resulted in a 15% improvement in EC at 8 weeks, which was sustained at 1 year (2). Despite the well-documented relationship between AF and EC, the mechanism is not fully understood. Here we focused on LA-TR as a unifying mechanism connecting EC and AF.

The LA modulates LV filling through 3 components: a phase of reservoir or expansion during systole, a conduit phase during diastole, and an active contractile component during late diastole (21). A loss of atrial contractile function, such as during AF, reduces cardiac output by approximately 15% to 20% at steady state (22,23). Furthermore, in patients with paroxysmal AF, LA strain and strain rate have been shown to be reduced even while in sinus rhythm (24,25). Successful catheter ablation of AF results in improved LA transport function, whereas patients with recurrent AF after ablation do not demonstrate reverse remodeling (4).

The mechanism of impaired transport function in patients with AF lies in tissue level electrical and mechanical remodeling of the LA. Patients with AF have extensive abnormalities in atrial ultrastructure. Initial studies in animal models showed remodeling in atrial ultrastructure and dedifferentiation of atrial myocytes to a more fetal stage after sustained atrial pacing (26,27). Similar changes were reported in human atrial tissue in patients with AF who were undergoing valve surgery and in patients with lone AF. These studies also showed that patients with AF had increased interstitial fibrosis. Mary-Rabine et al. (28) examined the relationship between atrial ultrastructural changes by using optical and electron microscopy and cellular electrophysiological derangements to clinical hemodynamic manifestations. Their study showed that the contractile force of the atria is reduced due to myolysis and to an imbalance in collagen synthesis and degradation.

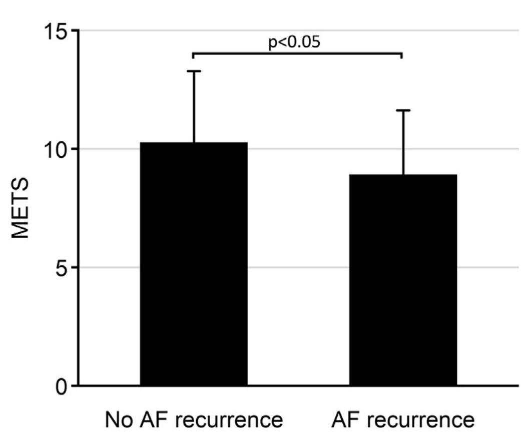
LGE-CMR offers unique advantages in the management of patients with AF. It allows visualization of structural changes in both left and right atria in patients with AF. Indeed, our group has previously reported on the role of LGE-CMR in aiding patient selection, prognostication, and treatment strategy in AF (13). The extent of enhancement on LGE-CMR has been shown to inversely correlate to markers of LA contractile function (strain and strain rate) (14).

FIGURE 3 Changes in Heart Rate and MET Level by Heart Rhythm at the Time of ETT



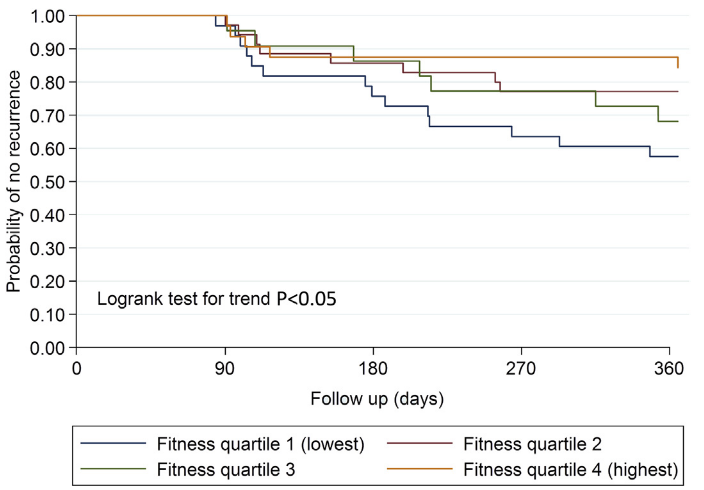
The p value remained significant when adjusting for baseline medications. AF = atrial fibrillation; ETT = exercise treadmill test; HR = heart rate; MET = metabolic equivalent; SR = sinus rhythm.

FIGURE 4 Mean MET Level Achieved at Baseline (Pre-Ablation) in Subjects With and Without AF Recurrence 1 Year After Catheter Ablation



Abbreviations as in Figure 3.

FIGURE 5 Kaplan-Meier Graph Shows AF Recurrence Over 365 Days' Follow-Up Stratified by Patients by Fitness Quartiles



Results from this study demonstrate that greater degrees of tissue LA-TR by LGE-CMR are associated with decreased EC. The underlying mechanism is most readily explained by altered LA transport function in patients with varying degrees of LA-TR. The MET level achieved on a treadmill is determined, at least in part, by preserved transport function during exercise. In patients with high degrees of LA-TR by CMR imaging (Utah Stages III and IV) this transport function is impaired to a greater degree than in patients with lower stages of remodeling (Utah Stage I and II). This has important clinical implications since patients with AF will often endorse fatigue as a prominent symptom. This may well be a reflection of diminished EC in these patients due to LA tissue remodeling. Visualization of tissue level changes by LGE-CMR imaging may aid in understanding the degree of functional limitation endorsed by the patient.

This study also demonstrates that baseline EC is associated with the outcome from AF ablation. These results can also be explained by preserved LA transport function in patients with greater EC at baseline. Previous work by Tops and colleagues, among others, has shown that preserved LA strain at baseline predicts reverse remodeling after AF catheter ablation (11). Moreover, preserved LA strain rate has been shown to predict the maintenance of sinus rhythm after catheter ablation (25). Therefore, it is consistent with prior work that greater degrees of EC predict the likelihood of freedom from AF after catheter ablation, to the extent that EC is influenced by LA transport function. In multivariate analysis, however, only LA-TR by LEG-CMR was predictive of ablation success to a significant degree. This probably reflects the fact that LA-TR is a more reliable and reproducible index of LA transport function than EC, which can be influenced by myriad factors at the time of testing.

STUDY LIMITATIONS. A limitation of our study was selection bias, as only those patients who were able to undergo treadmill testing were included in the analysis. This could have steered the study to include more healthy patients, thus excluding patients with severe functional limitation. Alternately, this may also be a strength of our work, since, with the relatively healthy cohort, we may have minimized the effect of comorbidities and thus possibly identified a more pure AF phenotype. Another limitation of the study lies in our relatively small sample size, which may lead to a lack of statistical significance when a physiologic signal may in fact exist. Thirdly, this is an observational retrospective chart review, which has inherent limitations.

CONCLUSIONS

Left atrial structural remodeling as seen by LGE-CMR is inversely related to EC in subjects with atrial fibrillation. Additionally, greater EC at baseline predicts freedom from atrial fibrillation after catheter ablation. Further research is needed to determine the exact mechanistic relationship between atrial fibrillation and EC.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Maximal exercise capacity is inversely associated with the degree of left atrial fibrosis in patients with atrial fibrillation. In addition, maximal exercise capacity is predictive of freedom from AF post ablation.

TRANSLATIONAL OUTLOOK: Additional prospective studies in larger populations are needed to assess the impact of left atrial fibrosis on maximal patient activity in patients with atrial fibrillation.

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