

Effect of Late Gadolinium Enhancement on the Recovery of Left Ventricular Systolic Function After Pulmonary Vein Isolation

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Background—The factors that predict recovery of left ventricular (LV) systolic dysfunction among patients with atrial fibrillation (AF) are not completely understood. Late gadolinium enhancement (LGE) of the LV has been reported among patients with AF, and we aimed to test whether the presence LGE was associated with subsequent recovery of LV systolic function among patients with AF and LV dysfunction.

Methods and Results—From a registry of 720 consecutive patients undergoing a cardiac magnetic resonance study prior to pulmonary vein isolation (PVI), patients with LV systolic dysfunction (ejection fraction [EF] <50%) were identified. The primary outcome was recovery of LVEF defined as an EF >50%; a secondary outcome was a combined outcome of subsequent heart failure (HF), admission, and death. Of 720 patients, 172 (24%) had an LVEF of <50% prior to PVI. The mean LVEF pre-PVI was $41 \pm 6\%$ (median 43%, range 20% to 49%). Forty-three patients (25%) had LGE (25 [58%] ischemic), and the extent of LGE was $7.5 \pm 4\%$ (2% to 19%). During follow-up (mean 42 months), 91 patients (53%) had recovery of LVEF, 68 (40%) had early recurrence of AF, 65 (38%) had late AF, 18 (5%) were admitted for HF, and 23 died (13%). Factors associated with nonrecovery of LVEF were older age, history of myocardial infarction, early AF recurrence, late AF recurrence, and LGE. In a multivariable model, the presence of LGE and any recurrence of AF had the strongest association with persistence of LV dysfunction. Additionally, all patients without recurrence of AF and LGE had normalization of LVEF, and recovery of LVEF was associated with reduced HF admissions and death.

Conclusions—In patients with AF and LV dysfunction undergoing PVI, the absence of LGE and AF recurrence are predictors of LVEF recovery and LVEF recovery in AF with associated reduction in subsequent death and heart failure. (*J Am Heart Assoc.* 2016;5:e003570 doi: 10.1161/JAHA.116.003570)

Key Words: atrial fibrillation • cardiac dysfunction • cardiovascular magnetic resonance imaging • heart failure • late gadolinium enhancement

There are significant epidemiological and mechanistic data linking atrial fibrillation (AF) and left ventricular (LV) dysfunction.¹ Atrial fibrillation is associated with impairment of cardiac function.^{2,3} Similarly, heart failure is associated with altered atrial mechanics⁴ and the development of AF.⁵ The combination of AF and LV dysfunction is consistently associated with an additive increase in morbidity and mortality over either condition alone.^{5,6} Recovery of LV dysfunction has been

observed after treatment of AF⁷⁻⁹; however, predicting which patients will recover LV function after successful treatment of AF remains an open and important clinical question.^{7,9-11} Pulmonary vein isolation (PVI) is a reasonable therapeutic option in patients with AF and LV dysfunction.¹² Observational and randomized studies have evaluated the role of PVI in improving LV function as compared to conventional medical therapy in patients with AF and LV dysfunction.^{9,10,13} However,

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An accompanying Figure S1 is available at <http://jaha.ahajournals.org/content/5/9/e003570/DC1/embed/inline-supplementary-material-1.pdf>

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the results have been inconsistent and suggest that better stratification of which patients with AF and LV dysfunction benefit most may be of benefit.

Late gadolinium enhancement (LGE) is associated with adverse outcomes in a variety of cardiovascular diseases.¹⁴⁻¹⁷ The presence and extent of LGE have been tied to LV recovery in patients after myocardial infarction¹⁸ and in those with dilated cardiomyopathies.¹⁹ However, there are limited data evaluating the prognostic impact of the presence (or absence) of LGE in patients with LV dysfunction and AF. Therefore, we sought to determine the prevalence, predictors, and prognostic significance of recovery of LV function in patients with AF undergoing PVI. We specifically address the role of LGE in identifying groups more or less likely to improve LV function after PVI.

Methods

Study Population

A cardiac magnetic resonance (CMR) study is the test of choice at our institution for imaging of the pulmonary veins prior to PVI. From a consecutive series of patients with AF who were referred for a CMR study between September 2005 and June 2011 for imaging of pulmonary vein anatomy, we identified those with a reduced LVEF. Patient and imaging variables were recorded at the time of the CMR using an on-line secure registry tool (CMRcoop) as previously described.²⁰ We did not exclude patients with a prior PVI. A reduced LVEF was defined as an LVEF on CMR of <50%.²¹ The Human Subjects Research Review Committee of our institution approved the study protocol. The requirement for informed consent was waived.

CMR Protocol

All images were acquired with electrocardiographic (ECG) gating, breath holding, and with the patient in a supine position as previously described.²⁰ The CMR protocol consisted of cine steady-state free precession (SSFP) imaging for cardiac function (typical repetition time, 3.4 milliseconds; echo time, 1.2 milliseconds; in-plane spatial resolution, 1.6×2 mm), pulmonary vein anatomy imaging, and LGE imaging (repetition time, 4.8 milliseconds; echo time, 1.3 milliseconds; inversion time, 200-300 milliseconds). For LGE imaging, a segmented inversion-recovery pulse sequence was used starting 10 to 15 minutes after a single bolus dose of 0.15 mmol/kg of gadolinium DTPA (Magnevist[®]; Bayer HealthCare, Hanover, NJ). Cine imaging and LV LGE imaging were obtained in 8 to 14 matching short-axis (8 mm thick with 0 mm spacing) and 3 radial long-axis planes.²² LGE extent was quantified by a semiautomatic detection method using a previously validated research tool (Mass Research, Leiden University Medical Center, Leiden, The Netherlands),

with the extent of LGE defined using the full-width at half-maximum (FWHM) criteria.²² The mass of LV LGE was measured in grams and was expressed as a percentage of the total LV mass. The distribution of LGE was characterized as subendocardial, transmural, midwall, epicardial, or focal/ involving the RV insertion points. Left atrial (LA) volumes, and among patients in SR at the time of the CMR study, LA active emptying fraction and LA passive emptying fraction (LAPEF) were measured as previously described.²³ Imaging of the LA for LGE was not performed.

Pulmonary Vein Isolation Protocol

The PVI protocol consisted of point-by-point radiofrequency ablation to encircle the left and right pulmonary veins or by the use of a cryoballoon catheter (Arctic Front, Medtronic Inc, Minneapolis, MN). In all cases, PVI was confirmed by recording within the veins using a circular multipolar catheter to confirm entrance block into the veins. For patients with persistent AF, additional linear left atrial ablations were performed in addition to PVI. Often, this consisted of linear ablations to create conduction block across the left atrial roof and along the region between the lateral mitral annulus and left inferior pulmonary vein.²⁴ Areas of complex fractionated electrograms during AF were also targeted for ablation. If sinus rhythm could not be restored with ablation alone, administration of ibutilide or external cardioversion was performed to restore sinus rhythm.

Outcome Measures and Methods of Clinical Follow-Up

The first outcome measure, recovery of LV systolic function, was defined as an EF of >50% on subsequent testing. Because this was a retrospective study, testing of LV function had been performed at the discretion of the primary cardiologist and not at prespecified intervals. All methods for documentation of LV function were reviewed from the time of the performance of the entry CMR study until the recording of the prespecified EF value of >50%. To ensure that all measures of EF were recorded, we reviewed the electronic medical record, all hospitalization records, all primary care visits, and all visits to any primary or referring cardiologist. When discordance in LVEF in follow-up existed between CMR and TTE, the CMR-derived LVEF was used. We defined early recurrence of AF as AF occurring ≤3 months after PVI and confirmed by either ECG or cardiac monitoring. We defined late recurrence of AF as AF occurring >3 months after PVI and also confirmed by either ECG or cardiac monitoring.¹² We ascertained patient mortality using the Social Security Death Index and reviewed electronic medical records of all patients. When electronic medical records of a patient provided

insufficient follow-up information, the primary provider of the patient was contacted regarding clinical events. Admission for heart failure was determined by 2 main methods: if the admission occurred within the Partners Health System, then by review of the electronic medical record; if the admission occurred outside of the Partners Health System, then by confirming the final diagnosis of heart failure with the primary provider, admitting physician, or referring cardiologist. Complete follow-up was available for all patients.

Statistical Analysis

Continuous data are presented as mean±SD. Comparisons between groups were performed with the use of an independent sample *t* test for continuous variables, the Fisher exact test for categorical variables, and the Wilcoxon rank-sum test for ordinal variables. We employed 2 regression models, a logistic regression model and an ordinary least-squares (OLS) regression model. Furthermore, we applied a stepwise approach for both regression models. All regression models included markers associated with LV dysfunction as independent variables, including age, sex, history of MI, LVEF, NYHA functional status, early recurrence of AF post-PVI, late recurrence of AF post-PVI, and the presence of LGE. In both regression models we tested the association between the independent variables and the 3 different descriptors of LV recovery: binary outcome of recovery of LV function or not (logistic model), absolute increase in EF (OLS model), and relative changes in EF (EF post/EF pre) from pre- to post-PVI (OLS model). Event curves for mortality and the combination of mortality and heart failure admissions were determined according to the Kaplan-Meier method, and comparisons of mortality rates were performed by the log-rank test. The stepwise regression model used a *P* value of >0.10 for exclusion; otherwise for all other analyses, a 2-tailed *P* value of <0.05 was considered significant. To test whether the use of CMR-derived LVEF as opposed to TTE-derived LVEF was associated with a measurement bias, we compared simultaneous measures of CMR-derived LVEF with TTE-derived LVEF. For the purposes of this study, we defined simultaneous as less than 1 week. Correlation between measures were compared with the Pearson correlation coefficient, and levels of agreement were compared using a Bland-Altman analysis. Stata 10.0 was used for statistical analysis (StataCorp LP, College Station, TX).

Results

Patient Characteristics

In total, 720 consecutive patients were referred for a CMR in preparation for PVI and the characteristics of the whole cohort were described in a prior publication.²⁰ Of these 720 patients, 172 had a reduced EF (24%). Of this final study

cohort of 172 patients, there were 139 males (81%) with an average age of 55±10 years (range 28-75 years; Table 1). Patients required a PVI at a median of 30 months after first symptomatic onset of AF (range 9 months to 7 years). The median time from CMR to PVI was 1 week (IQR 1-2.5 weeks). Of the 172 patients, 52 (30%) had paroxysmal AF, and 120 (70%) had persistent AF. Half of the patients had hypertension (86, 50%), 25 (15%) had diabetes, 30 (17%) had sleep apnea, and 11 (6%) had a history of MI by ECG or clinical history. The medications at the time of study are listed in Table 1; in brief, 152 patients (88%) were on a β-blocker, 147 (86%) were on an ACE inhibitor, 42 (24%) were on digoxin, 49 (29%) were on a loop diuretic, and 106 (62%) were on a class 3 antiarrhythmic. At the time of the initial CMR study, 66 (38%) of the 172 were in atrial fibrillation, 24 (14%) were in atrial flutter, and 82 (48%) were in sinus rhythm. The majority of patients were New York Heart Association functional class 2 (100, 58%).

Imaging Characteristics

The mean LV EF pre-PVI was 41±6% (median 43%, range 20% to 49%), and right ventricular EF was 47±9% (range 20% to 69%). By CMR, mean LV end-diastolic volume was 177±50 mL, mean LV mass indexed to body surface area was 73±12 g/m², and the mean right ventricular end-diastolic volume was 168±42 mL (Table 2). Forty-three patients (25%) had LGE. The pattern of LGE was ischemic in 25 patients (58%: transmural in 10 [23%] and subendocardial in 15 [35%]) and nonischemic in 42% (midmyocardial in 15 [35%], insertion point in 3 [7%], Table 2). The average extent of LGE was 7.5±4% (range from 2% to 19%).

Outcomes Measures

During the period of follow-up (42 months), 91 patients (53%) had recovery of LVEF after PVI (defined as an EF of >50%). The median time to documentation of recovery of LV function was 152 days (range 28-420 days). Overall, the median change in LVEF after PVI was +7% (interquartile range [IQR] −1% to +14%), the mean LV EF post-PVI was 49±11%, and the median LVEF post-PVI was 50% (IQR 40% to 58%). In 39 patients the follow-up imaging modality was CMR; in 133 it was transthoracic echocardiography. For patients who had follow-up measures of LVEF using both CMR and TTE (*n*=34), the mean LVEF by 2-D TTE was 48±14% versus 50±13% for CMR (*P*<0.001). The correlation between measures was excellent with an *r*=0.95 (*P*<0.001). There was an average difference between the measures of 3.6%, and the 95% limits of agreement ranged from −5% to +12% (Figure S1). During follow-up, 68 (40%) had early recurrence of AF, 65 (38%) had late AF, and there were 8 admissions for heart failure (5%) and 23 deaths (13%; Table 3). The median time to early recurrence

Table 1. Clinical Characteristics of All Patients, and Stratified According to Nonrecovery or Recovery of EF (EF < or ≥50%)

Variable	Cohort (N=172)	Nonrecovery of EF (N=81)	Recovery of EF (N=91)	P Value
Age, y, mean (SD)	55±10	57±10	53±10	0.01
Male	139 (81)	64 (79)	75 (82)	0.70
History of MI	11 (6)	9 (11)	2 (2)	0.03
Paroxysmal AF	52 (30)	23 (28)	29 (32)	0.74
Persistent AF	120 (70)	58 (72)	62 (68)	0.62
Prior AF ablation	41 (24)	22 (27)	19 (21)	0.37
Hypertension	86 (50)	45 (56)	41 (45)	0.22
Diabetes mellitus	25 (15)	10 (12)	15 (17)	0.52
Sleep apnea	30 (17)	13 (16)	17 (19)	0.69
Family history of AF	25 (15)	13 (16)	12 (13)	0.67
NYHA functional status				
1	66 (38)	36 (44)	30 (33)	0.16
2	100 (58)	43 (53)	57 (63)	0.22
3	6 (4)	2 (3)	4 (4)	0.69
Medications				
Aspirin	76 (44)	40 (49)	36 (40)	0.22
Clopidogrel	2 (1)	2 (3)	0 (00)	0.22
β-Blockade	152 (88)	71 (88)	81 (89)	0.82
Calcium channel blocker	26 (15)	13 (16)	13 (14)	0.83
ACE inhibitor	147 (86)	69 (85)	78 (86)	1.00
Class 3 antiarrhythmic				
Combined	106 (62)	50 (62)	56 (62)	1.00
Amiodarone	57 (54)	27 (54)	30 (53)	1.00
Sotalol	33 (31)	16 (32)	17 (31)	1.00
Dofetilide	16 (15)	7 (14)	9 (16)	1.00
Digoxin	42 (24)	20 (25)	22 (24)	1.00
Loop diuretic	49 (29)	24 (30)	25 (28)	0.87
Spironolactone	46 (27)	22 (27)	24 (26)	1.00
Statin therapy	63 (37)	32 (40)	31 (34)	0.53
Physical exam				
BMI, kg/m ² , mean±SD	29±5	29±5	29±4	0.75
BSA, m ² , mean±SD	2.1±0.2	2.1±0.2	2.1±0.2	0.33
Systolic BP, mm Hg, mean±SD	125±18	126±19	123±16	0.28
Diastolic BP, mm Hg, mean±SD	76±13	76±13	76±12	0.99
Heart rate, beats/min, mean±SD	78±18	79±18	78±19	0.61
Rhythm at the time of CMR				
Sinus rhythm	82 (48)	39 (48)	43 (47)	0.89
AF	66 (38)	29 (36)	37 (41)	0.54
Atrial flutter	24 (14)	13 (16)	11 (12)	0.52

All data are number and percentage unless otherwise specified; heart rate and blood pressure were obtained at the time of pre-PVI CMR. ACE indicates angiotensin-converting enzyme significance; AF, atrial fibrillation; BMI, body mass index; BSA, body surface area; CMR, cardiac magnetic resonance; EF, ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

Table 2. ECG and CMR Characteristics of All Patients, Stratified According to Nonrecovery or Recovery of EF (EF < or ≥50%)

Variable	Cohort (N=172)	Nonrecovery of EF (N=81)	Recovery of EF (N=91)	P Value
Electrocardiography				
Atrioventricular delay, ms	179±33	184±36	174±30	0.17
QRS duration, ms	98±17	98±16	98±18	0.87
QTc, ms	448±32	453±30	444±34	0.06
Q waves, n (%)	16 (9.3)	12 (14.8)	4 (4.4)	0.03
LVH, n (%)	13 (7.6)	7 (8.6)	6 (6.6)	0.77
Cardiac magnetic resonance				
LV EF, %	41±6	40±5	42±6	0.08
LVEDV, mL	177±50.3	176±47	177±50	0.95
LVESV, mL	107±50	105±32	109±63	0.61
LV mass, g	152±33	155±28	149±37	0.26
LV mass index, g/m ²	73±12	75±11	72±14	0.20
LVEDV index, mL/m ²	85±25	86±24	85±25	0.88
LVESV index mL/m ²	50±17	51±16	49±17	0.65
RVEDV, mL	168±42	166±46	170±39	0.58
RVESV, mL	92±30	90±33	94±28	0.45
RV EF, %	47±9	48±10	46±9	0.24
RVEDV index, mL/m ²	80±20	80±22	81±19	0.79
RVESV index, mL/m ²	44±14	43±16	45±13	0.45
LA dimension, mm	42±6	43±6	42±6	0.07
LAV max, mL	127±41	130±38	125±44	0.22
LAV min, mL	92±40	95±36	89±43	0.31
LA passive EF (%; n=82)	23±11	20±11	26±10	0.009
LA active EF (%; n=82)	23±13	23±13	22±12	0.72
Late gadolinium enhancement				
LGE presence, n (%)	43 (25)	39 (48)	4 (4)	<0.001
LGE extent, (% of LV)	7.4±4.1	7.7±4.2	4.6±1.0	0.001
LGE location, n (%)				
Midwall	15 (35)	13 (33)	2 (50)	<0.001
Insertion point	3 (7.0)	2 (5)	1 (25)	0.60
Subendocardial	15 (35)	14 (36)	1 (25)	<0.001
Transmural	10 (23)	10 (26)	0 (0)	<0.001

All data are mean and standard deviation unless otherwise specified. LVH=left ventricular hypertrophy by Sokolov-Lyon criteria. CMR indicates cardiac magnetic resonance; LA, left atrial; LAV, left atrial volume; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic volume; LVH, left ventricular hypertrophy; MI, myocardial infarction; NYHA, New York Heart Association; PVI, pulmonary vein isolation; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume.

was 1.5 months (IQR 0.5-2.5 months). The median time to late AF recurrence was 9 months (IQR 7-15.5 months).

Predictors of Recovery of LV Function

We compared nonimaging and imaging variables among patients with and without recovery of LV function (Tables 1

through 3). Patients with nonrecovery of LV function had a higher prevalence of myocardial infarction, a higher overall prevalence of LGE, and more extensive LGE, and they were more likely to have early and late recurrence of AF. Left atrial volume was similar in patients with and without recovery of LVEF. When patients with and without recovery of LV function were compared, the early AF recurrence rate was 28% among

Table 3. Outcome Characteristics of All Patients, Stratified According to Nonrecovery or Recovery of LVEF (EF < or ≥50%)

Variable	Cohort (N=172)	Nonrecovery of EF (N=81)	Recovery of EF (N=91)	P Value
Early AF recurrence, n (%)	68 (40)	43 (53)	25 (27)	0.001
Late AF recurrence, n (%)	65 (38)	47 (58)	18 (20)	<0.001
Admission for CHF, n (%)	18 (11)	14 (17)	4 (4)	0.01
Death, n (%)	23 (13)	20 (25)	3 (91)	<0.001

AF indicates atrial fibrillation; CHF, congestive heart failure; EF, ejection fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PVI, pulmonary vein isolation.

those with recovery of LVEF and 53% among patients without recovery of LVEF ($P=0.001$). Late AF recurrence rate was 58% (47 patients) among patients without recovery of LVEF as compared to 20% among patients with recovery of LVEF (18 patients; $P<0.001$). Using both logistic regression (Table 4) and ordinary least-squares regression, we tested the associations between variables and the binary outcome of recovery of LV function. We found that the 3 strongest and most consistent predictors of recovery of EF were absence of early recurrence of AF, absence of late recurrence of AF, and the absence of LGE. We also tested which variables were most associated with the greatest absolute gain in LVEF (Table 5), the greatest relative gain in LVEF (Table 6), and a significant change in LVEF (defined as an EF change of >10%).²⁵ In these analyses we found that absence of early recurrence of AF, absence of late recurrence of AF, and absence of myocardial scar by LGE imaging showed a consistent and strong association with recovery of LVEF. Figure 1 shows box plots with the median and quartiles of EF pre- and post-PVI among

Table 4. Odds of LVEF Recovery (EF ≥50%) Post-PVI

Independent Variables	Odds Ratio	Std Err	P Value	95% Confidence Interval
Male	1.18	0.77	0.80	0.33 to 4.23
Age	0.96	0.03	0.11	0.91 to 1.01
History of MI	0.31	0.34	0.29	0.04 to 2.71
LV EF	1.00	0.04	0.97	0.92 to 1.09
NYHA class	1.18	0.60	0.75	0.43 to 3.20
Early AF recurrence	0.05	0.03	<0.001	0.01 to 0.19
Late AF recurrence	0.03	0.02	<0.001	0.01 to 0.11
Late gadolinium enhancement	0.01	0.01	<0.001	0.00 to 0.04

AF indicates atrial fibrillation; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PVI, pulmonary vein isolation.

Table 5. Absolute Change in LVEF% (Post-PVI EF–Pre-PVI EF)

Independent Variables	Coefficient	Std Err	P Value	95% Confidence Interval
Male	2.28	1.85	0.22	–1.37 to 5.93
Age	0.04	0.07	0.62	–0.11 to 0.18
History of MI	–1.10	2.59	0.67	–6.22 to 4.02
NYHA class	2.31	1.50	0.12	–0.64 to 5.27
Early AF recurrence	–4.52	1.49	0.003	–7.46 to –1.57
Late AF recurrence	–7.10	1.49	<0.001	–10.05 to –4.16
Late gadolinium enhancement	–11.36	1.82	<0.001	–14.96 to –7.76

AF indicates atrial fibrillation; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PVI, pulmonary vein isolation.

patients with and without LGE (Figure 1A), with and without early recurrence of AF (Figure 1B), with and without late recurrence of AF (Figure 1C), and patients with and without any combination of the 3 factors (Figure 1D). The pre-PVI LVEF was lower among patients with LGE (LVEF $39\pm6\%$ versus $42\pm6\%$, with vs without LGE, $P=0.01$), otherwise, there was no statistically significant difference in pre-PVI LVEF among groups with and without early recurrence of AF, and with and without late recurrence of AF. There was an improvement in average EF pre- and post-PVI in patients who did not have LGE, early recurrence of AF, or late recurrence of AF; however, there were still a significant percentage of patients without these individual predictors who had residual LV dysfunction. For example, among the 129 patients without LGE, 43 patients (33%) had a residual LV dysfunction with EF less than 50% post-PVI. Similarly, among the 107 patients without late recurrence of AF, 34 patients (32%) had a residual

Table 6. Relative Change in LVEF% (Post EF/Pre EF)

Independent Variables	Coefficient	Std Err	P Value	95% Confidence Interval
Male	0.06	0.06	0.29	–0.05 to 0.17
Age	0.00	0.00	0.90	0.004 to 0.005
History of MI	–0.03	0.08	0.68	–0.19 to 0.13
NYHA class	0.09	0.05	0.04	0.00 to 0.19
Early AF recurrence	–0.09	0.05	0.05	–0.18 to 0.00
Late AF recurrence	–0.18	0.05	<0.000	–0.27 to –0.09
LGE	–0.28	0.06	<0.000	–0.39 to –0.17

AF indicates atrial fibrillation; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

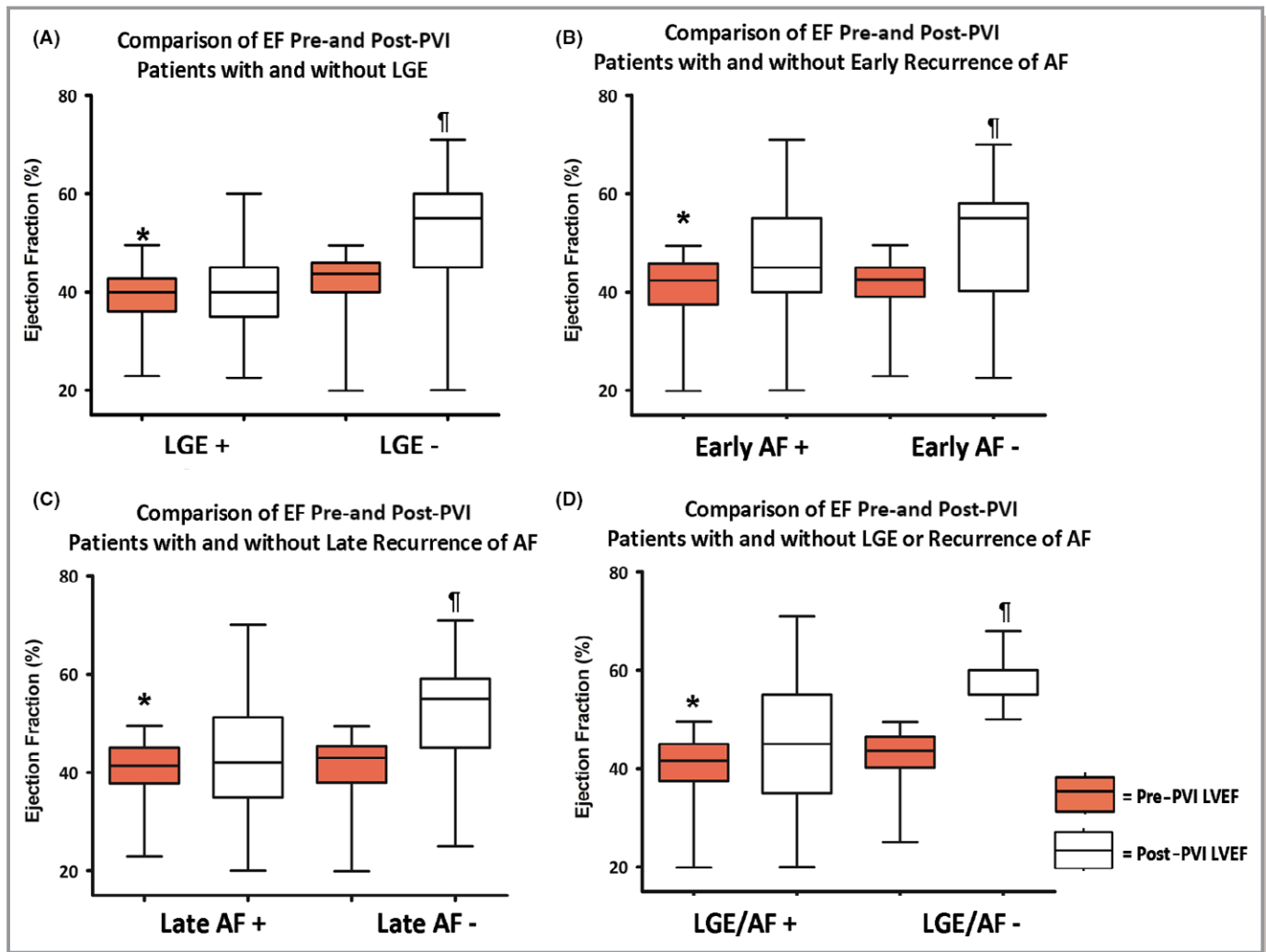


Figure 1. Box plots and confidence intervals comparing the pre-PVI LVEF to the post-PVI LVEF in patients with and without LGE (A), early recurrence of AF (B), late recurrence of AF (C), and without either LGE or any recurrence of AF (D). * $P=NS$ for comparison between pre-PVI LVEF among patients with and without LGE, early recurrence of AF, late recurrence of AF, and without either LGE or any recurrence of AF; † $P<0.001$ for comparison between post-PVI LVEF among patients with and without LGE, early recurrence of AF, late recurrence of AF, and without either LGE or any recurrence of AF. AF indicates atrial fibrillation; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation.

LVEF of less than 50%. In comparison, among patients without any of LGE, early AF recurrence, or late AF recurrence ($n=47$, 27% of the entire cohort), all had a residual EF of $>50\%$ (Figure 1D). To test whether the analyses are affected by patients with potential alternate causes of LV dysfunction, we also tested whether exclusion of patients with a prior MI by clinical history or ECG would affect the association between LGE, early AF recurrence, and late AF recurrence and recovery of LV function. After exclusion of patients with either a history of MI or ECG evidence of MI ($n=155$ after exclusion), we found that the absence of early AF recurrence, the lack of late AF recurrence, and the absence of LGE provided the strongest association with recovery of LV function. We also tested whether exclusion of patients with clinical history of MI, ECG evidence of MI, or LGE evidence of MI (transmural or

subendocardial LGE) would affect the association between LGE, early AF recurrence, and late AF recurrence with recovery of LV function. After exclusion of this extended subgroup ($n=142$ after exclusion), we found that the absence of early AF recurrence, the lack of late AF recurrence, and the absence of LGE still provided the strongest association with recovery of LV function. Finally, we also considered whether the incorporation of post-PVI CMRs for EF assessment would introduce a bias in that patients undergoing a CMR would be those more likely to have an AF recurrence, and the repeat CMR was prior to a planned repeat ablation. Therefore, we repeated the analysis using only patients with non-CMR-based repeat measures of LV function ($n=133$) and found that AF recurrence and LGE still provided the strongest association with recovery of LV function.

Table 7. Multivariable Cox Regression Models: Mortality and Mortality/CHF Admission

	Hazard Ratio	Std Err	P Value	95% Confidence Interval
Mortality				
EF ≥50%	0.28	0.19	0.064	0.07 to 1.08
LGE	3.28	1.53	0.011	1.31 to 8.17
Mortality/CHF admission				
EF ≥50%	0.41	0.21	0.081	0.15 to 1.12
LGE	4.01	1.61	0.001	1.83 to 8.80

CHF indicates congestive heart failure; EF, ejection fraction; LGE, late gadolinium enhancement.

Recovery of LV Function and Admission for Heart Failure and Death

Over a median follow-up time of 42 months (IQR 24-51), there were a total of 41 events; these included 23 deaths (mortality rate 4% per year) and 18 admissions for heart failure (3% per year). We found that among the 91 patients who had recovery of LV function, there were 3 deaths and 4 admissions for heart failure as compared to 20 deaths and 14 admissions for heart failure among the 81 patients who had persistence of LV dysfunction. We next tested the effect of inclusion of LGE in a multivariable model testing the association between the recovery of LVEF and the occurrence of an adverse event. In this multivariable model we found that the presence of LGE had the strongest association with the endpoint of mortality and the combined endpoint of mortality and CHF admission.

Furthermore, the association with recovery of LV function was no longer significant (Table 7). Kaplan-Meier plots showing the event rates for mortality (Figure 2A) and mortality and heart failure admission (Figure 2B) are shown.

Discussion

The principal findings of our study include (1) that nearly 53% of patients showed recovery of LV function after PVI, (2) that there is a robust association between both absence of LGE and AF recurrence and recovery of LV function post-PVI, and (3) that an association exists between the recovery of LV function in patients with AF and an improvement in mortality and a reduction in heart failure hospitalizations. In addition, we note that the association between recovery of LV function and adverse outcomes is primarily determined by the presence or absence of pre-PVI LGE, suggesting that the presence of LGE in patients with AF and reduced EF is an important preprocedure predictor of outcomes. Given the equipoise regarding the use of PVI in patients with AF and LV dysfunction (vs rate control), our results suggest that CMR-LGE may be used as a complementary biomarker to identify those patients most likely to benefit from PVI with the goal of improving LV function.

Our study provides important additive data detailing LV recovery in patients with AF.^{7,8,26-28} Importantly, baseline LV function, time to LV recovery, and quantitative improvement in LV function post-PVI were comparable to those seen in prior work in this population.^{7,27-29} Moreover, given the prevalent use of optimal HF pharmacotherapy in our cohort

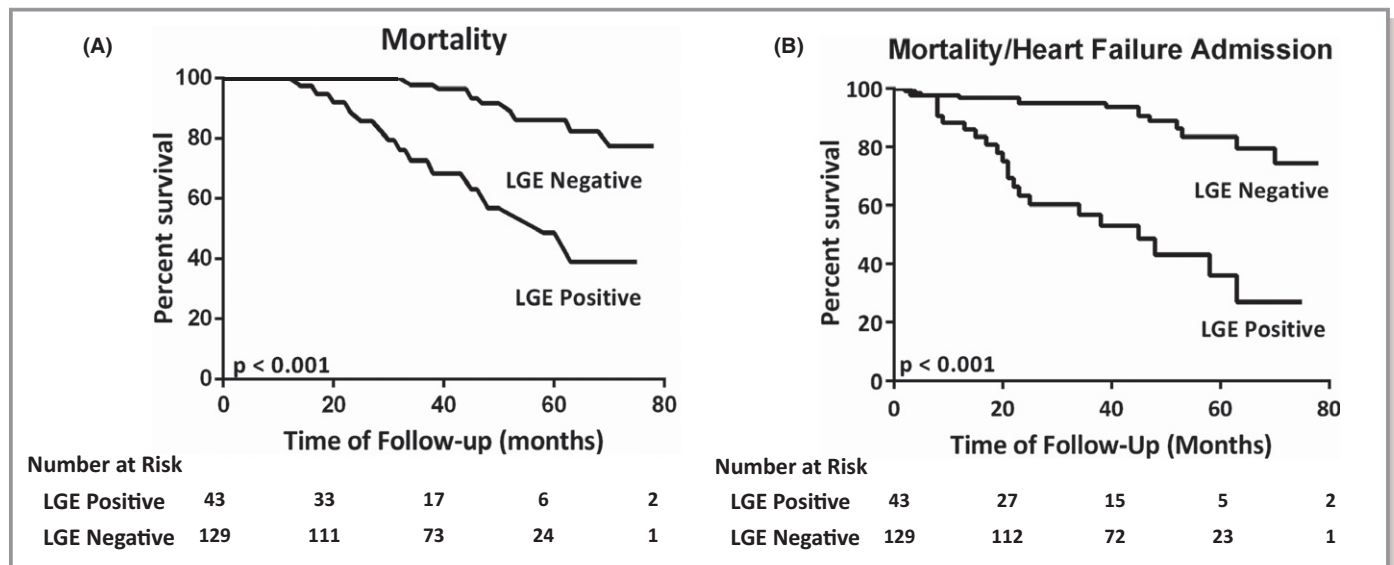


Figure 2. Kaplan-Meier curves displaying survival probability (A) and the combination of survival and heart failure admission (B) in the cohort of patients with AF and a reduced EF. The cohort is separated according to the presence or absence of LGE. Results were compared using a log-rank test with a P value of <0.001. LGE indicates late gadolinium enhancement.

(nearly 90% of patients were on β -blockade and ACE inhibition pre-PVI, with similar therapy in patients with and without recovery), the improvement in LVEF was not likely related to optimization of heart failure medications. Interestingly, although most studies assessing the effect of PVI on LV function in patients with AF and LV dysfunction have demonstrated an improvement in LVEF,³⁰ this is not a consistent finding, and we hypothesize that this may be in part owing to inclusion of patients with coronary disease (up to 80% of the referred population in 1 study). Specifically, in this study, we may provide a mechanism for the negative observation for studies such as that of Chen and colleagues.²⁸ We found that the presence of scar by LGE was associated with lack of LV recovery.³⁰ There are different patterns of LGE but LGE in a subendocardial or transmural pattern typically represents prior myocardial infarction. It is possible that a lack of LGE in patients with uncontrolled AF and coronary disease referred for PVI may identify a unique subgroup of patients with coronary disease in whom tachycardia may be a predominant etiology of reversible LV dysfunction (“tachycardia-mediated cardiomyopathy”) instead of predominantly ischemic cardiomyopathy with bystander AF or an irreversible cardiomyopathy with scar deposition.

We also found an association between AF recurrence and failure to improve LVEF. The association between recurrent AF and change in EF post-PVI is consistent with prior published data.^{10,26} However, there are limited data testing the role of preexisting LGE and improvement in LV function in patients prior to PVI.³¹ In a smaller study of 16 patients with LV dysfunction referred for PVI, Ling and colleagues found that all patients without LGE pre-PVI or recurrent AF at 6 months had normalized LV function post-PVI.³¹ Interestingly, in that study, the single patient who did not normalize LV function had AF recurrence. Our work provides additive evidence that both AF recurrence and LGE collaborate to prevent LV recovery post-PVI, suggesting the utility of CMR pre-PVI to identify those patients requiring closer clinical surveillance and/or intensification of HF therapy.

Data testing the effect of PVI on outcomes in patients with AF and a reduced EF are conflicting. Rhythm control strategies, using medical therapy, in comparison to rate control have not been associated with a mortality benefit in patients with AF and a reduced EF.¹¹ Interestingly, most of the heterogeneity in published work relates to the presence of concurrent coronary artery disease and efficacy of PVI, providing support that these parameters (eg, LGE and AF recurrence) are critical to LV recovery post-PVI. Suman-Horduna and colleagues demonstrated an improvement in symptoms without objective improvement in functional capacity with PVI,³² which has been recapitulated by other groups.⁹ Khan et al demonstrated that PVI with nodal ablation and cardiac resynchronization therapy in patients with AF and

a reduced EF³³ led to improvement in LV EF as well as functional status. In a complementary study, MacDonald and colleagues¹⁰ found PVI ineffective to promote LV recovery; however, a large fraction of their cohort had significant coronary disease, and only 50% of patients had a successful PVI. In the context of these and other³⁴ prior smaller studies, our results specify the phenotype of those patients with the highest chance of LV recovery after PVI with an imaging biomarker (LGE) that reflects underlying disease pathophysiology/HF etiology. These data also support continued efforts³⁵ to aggressively modify other risk factors including early inflammation associated with persistence of LV dysfunction post-PVI.

Limitations

This study should be interpreted within the context of its design. We recorded the medical therapy at the time of discharge after PVI, and the change in patient-specific antiarrhythmic therapy or heart failure medications over time was not included in this analysis. Furthermore, early AF recurrence, even if associated with late AF recurrence, does not preclude a successful long-term outcome. We did not factor in the subsequent change in pharmacological rhythm management as a result of early AF recurrence. In addition, routine extended rhythm monitoring was not done in all patients, and monitoring was left to the discretion of the treating physician, reflecting real-world practice at the time of the study. As a result, we likely underestimated the recurrence rate of AF both early and late after PVI. We were unable to determine the adequacy of rate control post-PVI, although higher rates (reflecting higher adrenergic tone) may have been associated with recurrent AF. However, the presence of LGE is not affected by rate control. Measurement of LV function was not performed at prespecified intervals. However, we repeated the analysis after adjusting from the time to the first EF measurement, time to last EF measurement, and the overall number of measurements, and the results were unchanged. Measurements were also not performed with a prespecified modality or by a study-appointed core laboratory, and there are acknowledged differences in EF estimation depending on both the measure and the rhythm at the time of measurement. Analysis of the initial measures of LV function was performed by the study team; however, most subsequent measures of LV function were performed by a non-study reader, which would have resulted in greater variability of the measure. Specifically, the measurement of the LVEF post-PVI was adjudicated as part of this study. Routine follow-up CMR was generally not performed, and the primary indication for the repeat CMR study among the 39 subjects was consideration for repeat PVI to exclude pulmonary vein stenosis and among those in whom

an ICD was being considered. Finally, given our focus on patients undergoing PVI, we have limited ability to comment on the potential prognostic role of LGE in AF patients managed with a non-PVI strategy alone.

Conclusion

PVI in patients with AF and underlying LV dysfunction is associated with greater than 50% likelihood for recovery of LV function postprocedure. This probability is significantly increased by the absence of LGE and the lack of post-PVI AF recurrence. In addition, the recovery of LV function post-PVI is associated with a reduction in mortality and hospitalization for heart failure. Yet, in accounting for the presence of LGE, the association of LVEF recovery and outcomes is no longer significant, suggesting that the presence or absence of LGE is a primary determinant of events in patients with AF and reduced EF undergoing PVI. These data suggest that CMR and specifically LGE may serve as a useful guide in prognosticating AF patients with LV dysfunction under consideration for PVI. Additional larger studies evaluating patient groups more likely to show improvement in LVEF following PVI are needed.

Authors' Contributions

Dr Mayrhofer performed the statistical analysis. Neilan, Shah, Farhad, Addison, Kwong, and Jerosch-Herold performed the CMR scans, LGE analysis, and manuscript development. John, Michaud, and Stevenson provided patients for the study. All authors read and approved the final manuscript.

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Disclosures

None.

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Supplemental Material

Figure S1.

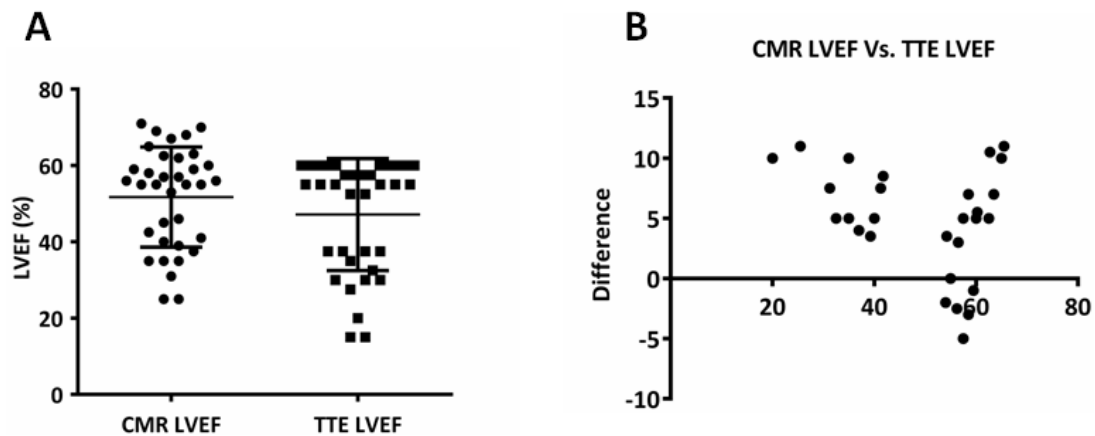


Figure Legend:

Figure S1: Box plots and confidence intervals comparing the post-PVI LVEF by CMR and TTE in those with a contemporary study (**A**) and a Bland Altman showing the agreement between the post-PVI LVEF by TTE and by CMR (**B**). For patients who had follow-up measures of LVEF using both CMR and TTE (n=34), the mean LVEF by 2-D TTE was $48 \pm 14\%$ vs. $50 \pm 13\%$ for CMR ($p < 0.001$). There was an average difference between the measures of 3.6% and the 95% limits of agreement ranged from -5% to +12%. Abbreviations: CMR = cardiac magnetic resonance; LVEF = left ventricular ejection fraction; TTE = transthoracic echocardiography.