JACC: CARDIOVASCULAR IMAGING
VOL. 9, NO. 2, 2016

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2015.05.011

ORIGINAL RESEARCH

Determinants of New-Onset Atrial Fibrillation in Patients Receiving CRT

Mechanistic Insights From Speckle Tracking Imaging

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the factors associated with the development of atrial fibrillation (AF) and to examine the impact of these factors for long-term outcome after cardiac resynchronization therapy (CRT).

BACKGROUND The effect of CRT on the development of new AF is under debate.

METHODS Clinical assessment, 12-lead electrocardiogram, echocardiography with speckle tracking strain imaging, and device interrogation before implantation and every 6 months thereafter were performed regularly over a 5-year follow-up. The primary endpoint was new-onset AF. Pre-specified outcome events were transplantation, assist device implantation, and death.

RESULTS During follow-up, AF occurred in 29 of 106 patients. Parameters of left atrial (LA) mechanics including mitral annular (A′) velocity, left atrial volume index (LAVI), LA ejection fraction, active emptying fraction, LA mean systolic strain (Ss) and late diastolic strain (Sa) improved at 6 months only in patients who remained free of AF. The change in LA Ss and Sa from baseline to 6 months after CRT had the highest accuracy to predict new-onset AF (area under the curve [AUC] = 0.793, 0.815, respectively, $p < 0.0001$ for both vs. left ventricular [LV] reverse remodeling AUC = 0.531; $p < 0.01$ for both). In addition, the change in LA Ss and Sa predicted outcome events independently from new-onset AF and LV volume response.

CONCLUSIONS LA functional improvement is essential for AF-free survival after CRT and is an independent predictor of AF-free survival. The improvement in LA Ss and Sa as a means of LA mechanical reserve also predicts long-term event-free survival after CRT independently from LV volume response and new-onset AF. (J Am Coll Cardiol Img 2016;9:99–111) © 2016 by the American College of Cardiology Foundation.

Patients with atrial fibrillation (AF) derive less outcome benefit than expected from cardiac resynchronization therapy (CRT), as observed in a European CRT survey and several other studies (1,2). AF is the most common reason for loss of effective pacing capture (3) and is a risk factor for mortality, appropriate shocks, and inappropriate shocks (4).

Left atrial (LA) reverse remodeling, as the biological basis for an atrial antiarrhythmic effect, occurred in patients who had CRT with defibrillators but not in patients with defibrillators only, in the MADIT-CRT (Multicenter Automated Defibrillator Implantation Trial-CRT) trial (5). However, there are conflicting results and scarce data about the effect of CRT on the incidence of AF (6–9). The discrepant results may partly reflect the different methods of AF surveillance. Some studies relied on symptomatic AF episodes or electrocardiograms, some relied on Holter monitor recordings, and some used device interrogation. Occurrence of short AF episodes may negate the real effect of CRT on AF burden and may not be relevant for the therapeutic effect of CRT (9).

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Manuscript received January 28, 2015; revised manuscript received April 24, 2015, accepted May 5, 2015.

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

3D = 3-dimensional

AF = atrial fibrillation

CRT = cardiac resynchronization therapy

E/E′ = ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity

EF = ejection fraction

LA = left atrium

LAVI = left atrial volume index

LV = left ventricular

MR = mitral regurgitation

Sa = late diastolic strain

Ss = systolic strain

In addition, several factors including LA mechanics, left ventricular (LV) diastolic function, LA pacing, and mitral regurgitation (MR) may affect the development of AF in patients who have had CRT. Accordingly, we examined systematically the potential factors associated with the development of new AF after CRT in patients without known previous AF, and we tested the hypothesis that atrial mechanical reserve, as assessed by changes in atrial deformation and reverse remodeling after CRT, is essential for AF-free survival.

METHODS

PATIENT POPULATION. Patients with heart failure in normal sinus rhythm who underwent CRT according to current guidelines were prospectively studied. Patients were excluded if they had chronic AF, no optimal medical therapy, inadequate images, prosthetic valves, unstable clinical conditions, or antiarrhythmic treatment other than beta-blockers. All patients underwent the following: clinical assessment; complete physical examination; conventional 2-dimensional (2D) Doppler, and tissue Doppler echocardiography; and device interrogation before implantation and every 6 months thereafter. The study protocol was approved by the Institutional Review Board and complies with the Declaration of Helsinki.

SEE PAGE 112

DEVICE IMPLANTATION. Biventricular device implantation was carried out using a transvenous approach with the right ventricular lead placed at the right ventricular apex and the LV lead targeting the lateral or posterolateral epicardial vein. All patients underwent atrioventricular delay optimization before discharge. All devices were programmed to the DDDR mode with a lower rate of 60 beats/min and an atrial high rate detection cutoff of 180 beats/min. Atrial bipolar sensitivity was programmed to one-half of the P-wave detected by the device with lowest values >0.25 mV. The high rate onset detection number of beats was 12, and the termination number was 12 consecutive beats at a rate higher and lower than the detection rate, respectively.

ECHOCARDIOGRAPHY. Images were obtained with cardiac ultrasound machines (Vivid *i*, General Electric, Haifa, Israel, and Vivid E9, General Electric, Horten, Norway) equipped with 3S-RS (1.5- to 3.6-MHz) and M5S-D (1.5- to 4.6-MHz) probes, respectively. Gray-scale digital cine-loops triggered to QRS complexes were acquired from apical 4-chamber, 2-chamber, and long-axis views, as well as from the mid-LV short-axis view. Three consecutive cardiac cycles were acquired during a breath-hold period at 60 to 100 frames/s and were digitally stored for off-line analysis using commercial software (EchoPAC PC SWO version 112.xx, General Electric, Horten, Norway) by researchers not involved in the clinical follow-up.

LV volumes and ejection fractions (EFs) were assessed using the modified Simpson rule. MR volume was estimated with the proximal isovelocity surface area method. Septal and lateral mitral annular velocities (E′, A′) were obtained by pulsed-wave tissue Doppler imaging and were averaged. Diastolic function was graded as abnormal relaxation, pseudonormal, and restrictive filling patterns, as previously described (10). LV mass quantification was performed from end-diastolic 2D images by using the area-length method.

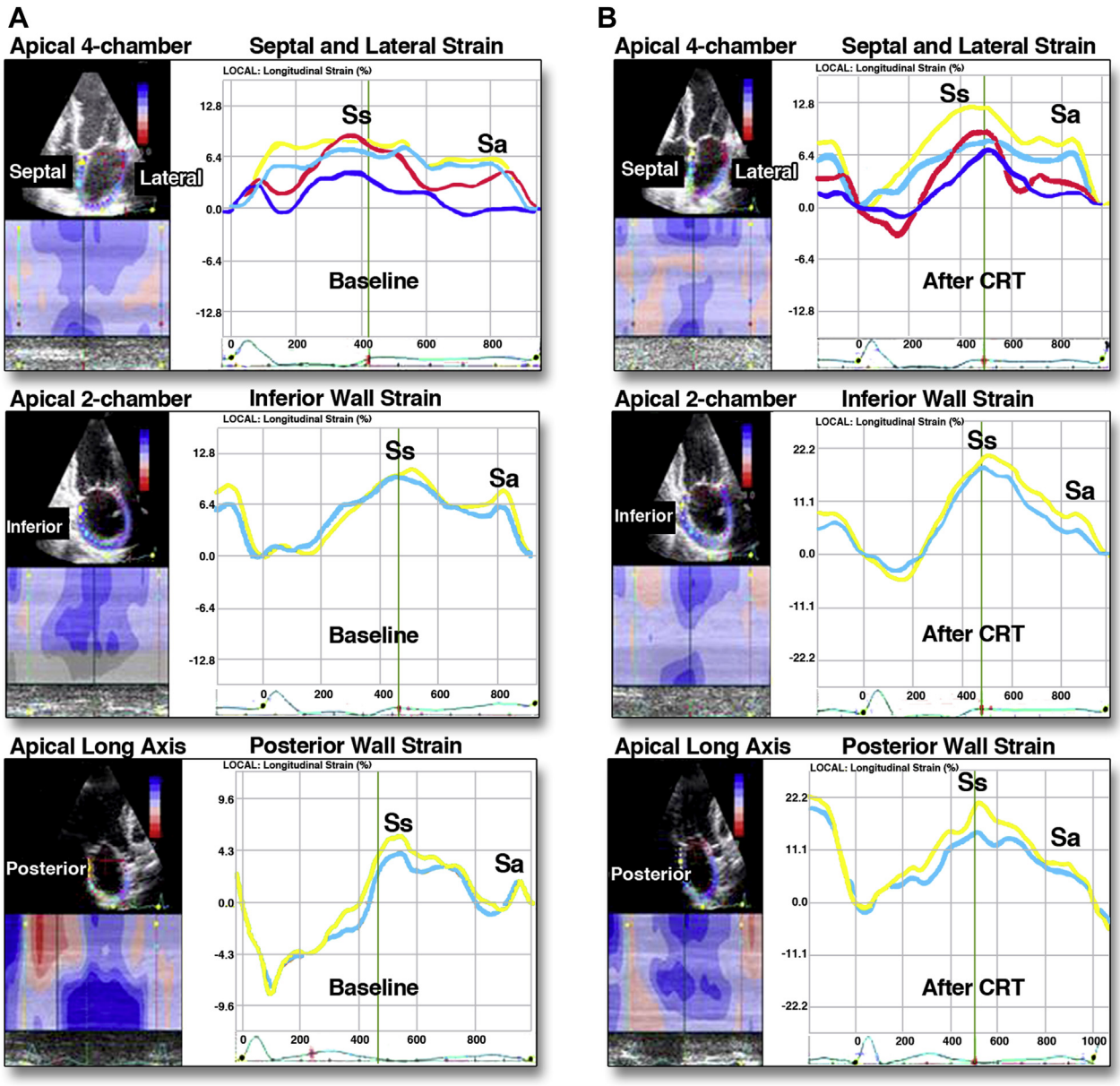
For 2D speckle tracking strain analysis, a curved region of interest was traced on the endocardial border in the apical 4-chamber, 2-chamber, and long-axis views of the left atrium and in the mid-LV short-axis view. From the traced endocardium a region of interest was automatically constructed approximating the myocardial wall, and it was adjusted as needed to fit the wall thickness. Regional strain was calculated as: length÷initial length by automated tracking of the location shifts of the acoustic markers in the myocardium. From the mid-LV short-axis view, radial dyssynchrony was measured as the delay between the peaks of septal and posterior wall strain curves (11).

ASSESSMENT OF ATRIAL MECHANICS. Using the modified Simpson rule, LA volume at ventricular end-systole (maximal LA volume), LA volume just before the beginning of atrial systole (Va) using the onset of P wave of the electrocardiogram as reference, and minimal LA volume were measured from apical 4-chamber and 2-chamber views. LA EF was calculated as: ([LA maximal volume − LA minimal volume] / LA maximal volume), and active emptying fraction was calculated as: ([Va − LA minimal volume] / Va). From the traced region of interest for 2D strain analysis, atrial time-strain curves were obtained from 6 regions (2 from each atrial wall and 2 from the atrial roof) in each apical view. Two regional time-strain curves from each of the following were averaged: the interatrial septum and the lateral (apical 4-chamber), inferior (apical 2-chamber), and posterior walls (apical long axis) of the left atrium. Atrial peak strain at ventricular end-systole (Ss) and at ventricular late diastole (using the onset of P-wave) (Sa) were measured as previously defined (12). Thus LA EF

and Ss corresponded to atrial reservoir function, and LA active emptying fraction and Sa corresponded to atrial contraction function. The anterior LA wall, because of interruption by the LA appendix and pulmonary vein ostium in the apical 2-chamber view, and the LA wall adjacent to the aorta in the apical long-axis view were not included in the strain analysis (Figure 1).

PRIMARY ENDPOINT AND OUTCOME EVENTS. The primary endpoint was the development of new AF, which is limited to either paroxysmal episodes lasting more than 24 h or persistent or permanent AF according to guidelines (13). Patients were regularly followed up every 6 months at the outpatient clinic after CRT implantation or were evaluated between scheduled visits whenever they had worsening

FIGURE 1 Left Atrial Strain Measurements by Speckle Tracking



Systolic strain (Ss) and late diastolic strain (Sa) before **(A)** and 6 months after **(B)** cardiac resynchronization therapy (CRT) in a patient without atrial fibrillation showing significant improvement.

symptoms. AF was defined as any episode of AF detected by the electrocardiogram or as sustained atrial high rate episodes with a maximum atrial rate of at least >180 beats/min detected by the device. Stored electrograms were examined to ensure that mode-switching episodes represented true AF episodes. The electrophysiologist responsible for device interrogation was blinded to the echocardiography data. AF episodes that occurred after implantation during the follow-up period, that fulfilled the foregoing criteria, and that were detected either by pacemaker interrogation or by findings during the clinical visits were taken into consideration for statistical analyses.

The outcome events for terminating follow-up were death, heart transplantation, or assist device implantation. Patients were censored for AF development at these pre-specified outcome events. Long-term follow-up after CRT was tracked up to 5 years.

STATISTICAL ANALYSES. Data are presented as mean ± SD for continuous variables or as percentage for categorical variables unless otherwise mentioned.

TABLE 1 Baseline Clinical Characteristics

	No New AF (n = 77)	New AF (n = 29)	p Value
Female	17	21	NS
Age, yrs	62 ± 11	62 ±11	NS
QRS duration, ms	145 ± 21	144 ± 23	NS
LBBB/RBBB/IVCD	61/9/30	75/11/14	NS
Posterolateral CS lead localization	79	69	NS
Ischemic origin	55	64	NS
Previous CABG	34	35	NS
Diabetes	31	32	NS
Hypertension	42	36	NS
Chronic kidney disease	21	25	NS
Upgrade from RV pacing	4	8	NS
Atrial pacing	7 (3–31)	23 (7–82)	0.013*
NYHA functional class II/III/IV	14/82/4	4/92/4	NS
Diastolic function			
Grade I	16	15	NS
Grade II	55	44	
Grade III	29	41	
ACEI/ARB use	92	86	NS
Beta-blocker use	89	96	NS
Aldosterone antagonist use	74	84	NS
Diuretic use	80	90	NS
Digoxin use	64	80	NS

Values are % or mean ± SD. *Mann-Whitney *U* test.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; CS = coronary sinus; IVCD = intraventricular conduction delay; LBBB = left bundle branch block; NS = not significant; NYHA = New York Heart Association; RBBB = right bundle branch block; RV = right ventricular.

Continuous and categorical variables between independent groups were compared using the Student *t* test or chi-square test, respectively. Continuous variables before and after CRT were compared by paired-samples Student *t* test. For variables with no normal distribution, the Mann-Whitney *U* test for independent samples and the Wilcoxon test for paired samples were used.

We tested several echocardiographic parameters as potential predictors of LA reverse remodeling in a multivariate linear regression model. Survival curves were obtained by the Kaplan-Meier method and were compared with log-rank test. To determine the predictors of new-onset AF, Cox regression analysis was conducted. Parameters with a p value <0.1 in the univariate analysis were entered into a multiple stepwise regression model as covariates. To avoid multicolinearity among the univariate predictors, a correlation coefficient of <0.7 was set. The correlation coefficients between LA EF and LA active emptying fraction were 0.80 and 0.78 at baseline and at 6 months and between LA mean Ss and Sa they were 0.76 and 0.87 at baseline and at 6 months, respectively. The correlation coefficient between the changes in Ss and Sa from baseline to 6 months was 0.73. Accordingly, these parameters were evaluated separately in multivariate models for their independent predictive value. The Cox proportional hazards model was used to determine the independent value of LA strain for the outcome by entering, new-onset AF and LV and LA volume parameters as fixed covariates.

Sensitivity and specificity of cutoff values of the parameters other than end-systolic volume change for new AF development were determined by receiver-operating characteristic curves by the Youden index, and areas under the curves were compared by the method of DeLong et al. (14). Changes of serial measurements over time in function of AF were studied by a general linear model. Intraobserver and interobserver variabilities for speckle tracking measurements were tested in 15 randomly selected patients using the identical cine-loops for each view and were calculated as the absolute differences divided by the mean value of the measurements and expressed as percentages. A 2-sided p value of <0.05 was considered significant. We used SPSS statistical software for Windows (version 15.0, SPSS Inc., Chicago, Illinois).

RESULTS

Of 112 patients, 6 did not return to any visit after discharge. We know that they were alive only by

TABLE 2 Echocardiographic Parameters at Baseline and 6 Months After CRT

	No New AF (n = 77)	New AF (n = 27)	p Value
LV EF baseline, %	22.8 ± 5.9	22.1 ± 5.8	NS
6-month follow-up, %	32.2 ± 10.3	29.1 ± 8.6	NS
p value	<0.0001	<0.0001	—
% change	38.5 (19 to 61)	24.4 (0 to 72)	NS*
LV ESVI baseline, ml/m^2	90 ± 35	91 ± 35	NS
6-month follow-up, ml/m^2	73 ± 37	74 ± 33	NS
p value	<0.0001	<0.0001	—
% change	16.7 (9.4 to 30.4)	14.5 (4 to 26.8)	NS*
LV mass baseline, g/m^2	146 ± 35	143 ± 37	NS
6-month follow-up, g/m^2	142 ± 38	138 ± 37	NS
p value	NS	NS	—
% change	-1.3 (-13.7 to 6.8)	-0.7 (-8.6 to 7.2)	NS*
Mitral regurgitation baseline, ml	21 (11 to 36)	30 (21 to 48)	0.05*
6-month follow-up, ml	15 (9 to 30)	23 (14 to 32)	NS*
p value	0.02†	0.03†	—
% change	-18.3 (-43.2 to 3.8)	-17.4 (-37 to 0)	NS*
E/E′ baseline	14.3 (10 to 19.3)	16.4 (13.7 to 23.3)	NS*
6-month follow-up	10.9 (8.8 to 16)	14.1 (11 to 21)	0.04*
p value	0.003†	0.04†	—
% change	-10.7 (-40 to 17.4)	-22.2 (-41.5 to 5)	NS*
A′ baseline, cm/s	5.4 ± 2.5	4.3 ± 1.6	NS
6-month follow-up, cm/s	6.3 ± 3.3	4.6 ± 1.9	0.01
p value	0.01	NS	—
% change	0 (-13.8 to 38.2)	0 (-20.8 to 31)	NS*
Radial dyssynchrony baseline, ms	182 ± 99	163 ± 67	NS
6-month follow-up, ms	72 ± 60	85 ± 79	NS
p value	0.0001	0.002	—
% change	-67.1 (-83.9 to 26)	-65.5 (-80.2 to 26.8)	NS*
InterV dyssynchrony baseline, ms	33 (15 to 61)	20 (10 to 60)	NS*
6-month follow-up, ms	17 (10 to 31)	12 (6 to 39)	NS*
p value	<0.001†	NS†	—
% change	-57.5 (-79.3 to -15.0)	-22 (-72.7 to 20.0)	NS*
LAVI baseline, ml/m^2	36 ± 11	40 ± 12	NS
6-month follow-up, ml/m^2	32 ± 10	41 ± 13	0.0001
p value	0.0001	NS	—
% change	-12.2 (-25.3 to 0.5)	4.8 (-8.7 to 11.2)	0.001*
LA EF baseline, %	43.5 ± 14.0	35.8 ± 16.0	0.02
6-month follow-up, %	48 ± 16	32 ± 13	<0.0001
p value	0.001	NS	—
% change	9.1 (-7.4 to 26)	-15.9 (-27.4 to 10.3)	0.015*
LA active emptying baseline, %	25 ± 13	20 ± 12	NS
6-month follow-up, %	30 ± 16	17 ± 16	0.001
p value	0.013	NS	—
% change	19.6 (-26 to 68)	-35.3 (-48.7 to 29.2)	0.017*
LA mean Ss baseline, %	18.2 ± 9.3	14.6 ± 6.0	NS
6-month follow-up, %	22.1 ± 10.7	14.1 ± 5.4	0.001
p value	0.0001	NS	—
% change	23.2 (6.9 to 54.2)	-11.9 (-22.3 to 1.1)	0.001*
LA mean Sa baseline, %	9.5 ± 4.9	7.6 ± 3.4	NS
6-month follow-up, %	12.1 ± 5.9	6.5 ± 3.0	<0.001
p value	0.001	NS	—
% change	26.7 (-3.3 to 70)	-19.1 (-33.3 to 0.8)	0.001*

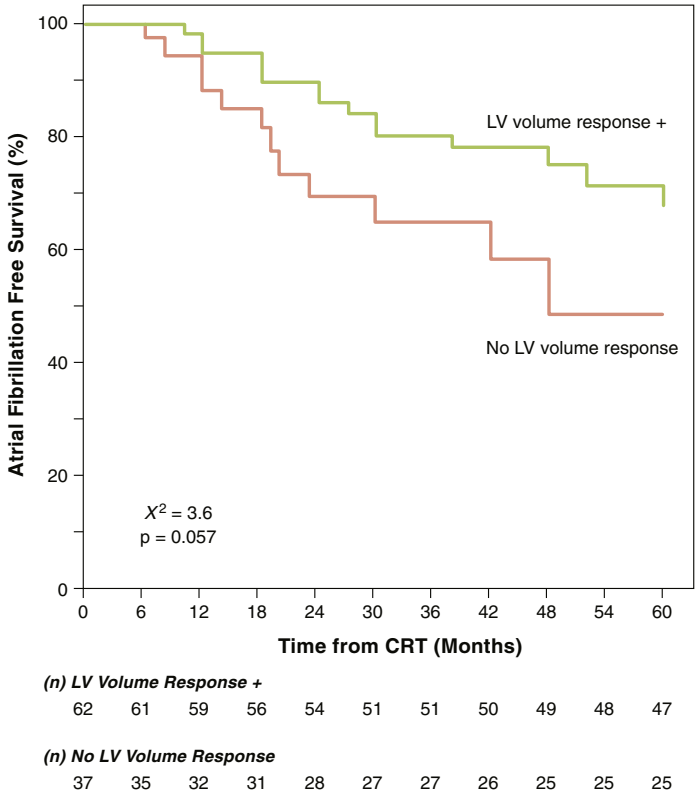
Values are mean ± SD or median (interquartile range). *Mann-Whitney *U* test; †Wilcoxon.

A′ = late diastolic mitral annular velocity; CRT = cardiac resynchronization therapy; E/E′ = ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity; EF = ejection fraction; ESVI = end-systolic volume index; InterV = interventricular, LA = left atrium; LAVI = left atrial volume index; LV = left ventricular; NS = not significant; Sa = late diastolic strain; Ss = systolic strain.

telephone contact but are not aware of their arrhythmias. In the remaining 106 patients, mean follow-up duration was 38 ± 19 months (median 42 months), new-onset AF occurred in 29 (27.4%) during follow-up, and 9 underwent atrioventricular node ablation to ensure an adequate ventricular pacing rate of more than 95%. In 2 patients AF occurred before 6 months of CRT. Accordingly, these patients were excluded from analyses relating to 6-month echocardiographic parameters. Baseline clinical characteristics of the patients are given in Table 1. The percentage of atrial pacing was significantly higher in patients who developed AF.

Intraobserver and interobserver variabilities of LA Ss and LA Sa were 6.5 ± 3.8% and 8.7 ± 6.1% for Ss and 10.8 ± 7.9% and 12.1 ± 6.5% for Sa, respectively. Echocardiographic parameters at baseline and 6 months after CRT are given in Table 2. MR was more important, and LA EF was lower at baseline in patients who developed new AF. After 6 months of CRT, LV end-systolic volume index, LV EF, MR volume, E/E′ (ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity), and radial dyssynchrony improved in patients with and without new-onset AF. However, parameters that indicated LA mechanics directly, including mitral annular late diastolic velocity (A′), left atrial volume index (LAVI), LA EF, LA active emptying fraction, and mean Ss and Sa, improved only in patients who remained in sinus rhythm.

FIGURE 2 Kaplan-Meier Survival Plot of Probability of AF-Free Survival After CRT in Function of LV Volume Response



During follow-up, 22.6% of patients with left ventricular (LV) volume response versus 32.4% without LV volume response developed atrial fibrillation. CRT = cardiac resynchronization therapy.

DETERMINANTS OF LA REVERSE REMODELING AND FUNCTION AFTER CARDIAC RESYNCHRONIZATION THERAPY. A multivariate linear regression analysis including the most pertinent variables (percentage of LA pacing and changes in MR, E/E′, A′, LV end-systolic volume, LV mass, and mechanical dyssynchrony by 6 months of CRT) was conducted to evaluate independent determinants of LA reverse remodeling and changes in Ss, and Sa. The decrease in MR emerged as the independent determinant of LA reverse remodeling ($p = 0.017$; 95% confidence interval [CI]: 0.032 to 0.321). The decrease in LV end-systolic volume ($p = 0.009$; 95% CI: 0.025 to 0.170) and the decrease in E/E′ ($p = 0.027$; 95% CI: 0.026 to 0.413) were independently associated with the improvement in LA Ss, whereas only the decrease in E/E′ was independently associated with the improvement in LA Sa ($p = 0.02$; 95% CI: 0.029 to 0.306).

PREDICTION OF ATRIAL FIBRILLATION AND OUTCOME AFTER CARDIAC RESYNCHRONIZATION THERAPY. During follow-up, 32 patients died, 2 underwent LV assist device implantation, and 1 underwent heart transplantation. Five of these events occurred within 6 months. Among survivors beyond 6 months ($n = 101$), LV volume response with >15% decrease in end-systolic volume was observed in 61% of the patients and was associated with a favorable effect on new-onset AF. After further excluding 2 patients who had AF before 6 months, AF developed in 14 of 62 (22.6%) with LV volume response and in 12 of 37 (32.4%) without LV volume response to CRT ($p = 0.057$) (Figure 2). Including the most pertinent variables in a Cox regression model to evaluate independent determinants of new-onset AF, among the baseline parameters, MR volume, percentage of atrial pacing, and LAVI, among the 6-month follow-up parameters, LAVI, LA Ss, and LA Sa were found to be independent predictors of new AF development. In addition, the changes from baseline to 6 months after CRT in LAVI, LA Ss, and LA Sa emerged as independent predictors of new AF development (Table 3). Among these variables, LAVI, Ss, and Sa at

6 months and the changes in these variables from baseline to 6 months after CRT had the highest accuracy to predict new-onset AF irrespective of LV volume response (Figures 3 and 4).

New-onset AF was associated with worse outcome as a univariate predictor but not as an independent predictor in multivariate models including LAVI, LV volume, LA Ss, and LA Sa. The 5-year event-free survival rate was 75% in patients free of AF as compared with 44% in patients with new-onset AF (log rank $p = 0.04$). However, LA Ss and Sa at 6 months and the change in LA Ss and Sa from baseline to 6 months after CRT predicted adverse events independently from new-onset AF and LA and LV volume changes (Table 4, Figure 5). Figure 6 summarizes the independent predictors of new-onset AF and survival after CRT.

We also examined the changes in LV volumes, EF, E/E′, and MR volume over time in function of AF in 71 patients who survived beyond 24 months. The development of AF was associated with gradual

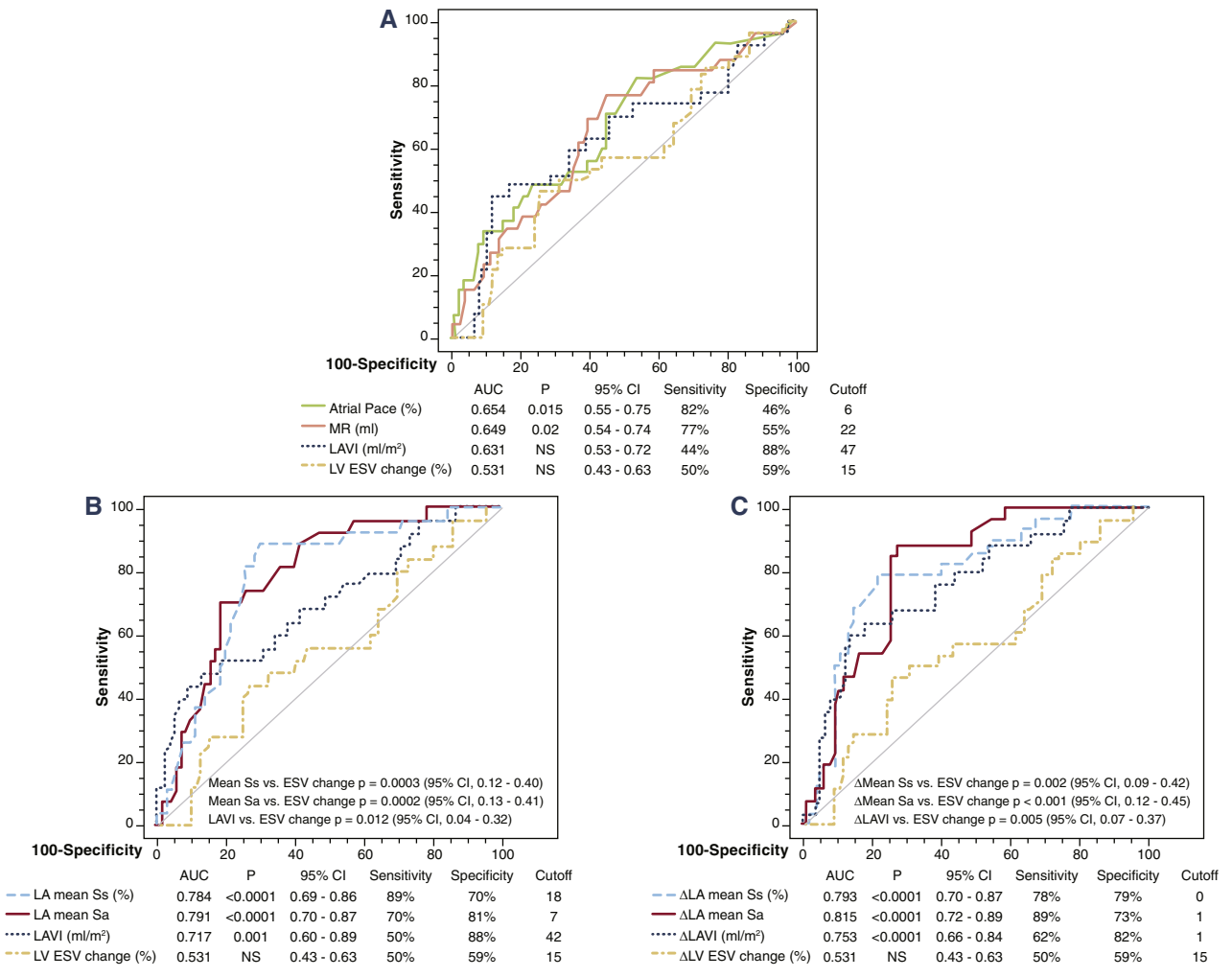
TABLE 3 Univariate and Multivariate Cox Regression Analysis to Predict New-Onset AF Using Baseline, 6-Month, and 6-Month Change Data

	Univariate		Multivariate*			
			Model 1		Model 2	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Baseline						
Atrial pacing, %	1.01 (1.00–1.02)	0.05	1.01 (1.00–1.02)	0.046	1.01 (1.00–1.03)	0.046
Mitral regurgitation, ml	1.04 (1.02–1.06)	<0.0001	1.04 (1.01–1.07)	0.005	1.04 (1.01–1.07)	0.005
InterV delay, ms	0.99 (0.99–1.01)	NS	–	–	–	–
Radial dyssynchrony, ms	0.99 (0.99–1.00)	NS	–	–	–	–
ESVI, ml/m^2	1.00 (0.99–1.01)	NS	–	–	–	–
E/E′	1.07 (1.01–1.13)	0.02	–	–	–	–
A′, cm/s	0.83 (0.68–1.01)	NS	–	–	–	–
LAVI, ml/m^2	1.06 (1.02–1.10)	0.003	1.05 (1.00–1.10)	0.03	1.05 (1.00–1.1)	0.03
LA active emptying, %	0.96 (0.92–0.99)	0.01	–	–	Not included	–
LA ejection fraction, %	0.95 (0.92–0.99)	0.004	Not included	–	–	–
Mean LA Ss, %	0.93 (0.88–0.99)	0.03	–	–	Not included	–
Mean LA Sa, %	0.91 (0.83–0.99)	0.03	Not included	–	–	–
Follow-up at 6 months						
MR, ml	1.03 (1.01–1.05)	0.01	–	–	–	–
InterV delay, ms	1.01 (0.99–1.03)	NS	–	–	–	–
Radial dyssynchrony, ms	1.00 (0.99–1.01)	NS	–	–	–	–
ESV, I ml/m^2	1.00 (0.99–1.02)	NS	–	–	–	–
E/E′	1.09 (1.03–1.14)	0.001	–	–	–	–
A′, cm/s	0.79 (0.67–0.94)	0.004	–	–	–	–
LAVI, ml/m^2	1.09 (1.05–1.13)	<0.0001	1.06 (1.02–1.10)	0.005	1.06 (1.02–1.10)	0.004
Active emptying, %	0.94 (0.91–0.97)	<0.0001	–	–	Not included	–
LA EF, %	0.93 (0.90–0.95)	<0.0001	Not included	–	–	–
Mean LA Ss, %	0.88 (0.83–0.94)	<0.0001	0.92 (0.86–0.98)	0.01	Not included	–
Mean LA Sa, %	0.78 (0.69–0.87)	<0.0001	Not included		0.87 (0.76–0.99)	0.003
Change from baseline to 6 months						
ΔMR, ml	1.0 (1.97–1.04)	NS	–	–	–	–
ΔInterV delay, ms	0.99 (0.98–1.00)	NS	–	–	–	–
ΔRadial dyssynchrony, ms	0.99 (0.99–1.01)	NS	–	–	–	–
ΔESVI, ml/m^2	0.98 (0.95–1.00)	NS	–	–	–	–
ΔE/E′	0.99 (0.93–1.04)	NS	–	–	–	–
ΔA′, cm/s	0.88 (0.74–1.04)	NS	–	–	–	–
ΔLAVI, ml/m^2	0.92 (0.88–0.97)	<0.001	0.95 (0.90–0.99)	0.04	–	–
ΔActive emptying, %	0.97 (0.94–0.99)	0.04	–	–	–	–
ΔLA EF, %	0.94 (0.91–0.98)	<0.0001	–	–	–	–
ΔMean LA Ss, %	0.82 (0.75–0.89)	<0.0001	0.85 (0.77–0.93)	0.001	Not included	–
ΔMean LA Sa, %	0.77 (0.69–0.85)	<0.0001	Not included	–	0.77 (0.69–0.86)	0.0001

*In multivariate models 1 and 2, parameters with a correlation coefficient ≥0.70 are evaluated separately to avoid multicolinearity.

AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio; Δ = change from baseline to 6 months after cardiac resynchronization therapy; other abbreviations as in Table 2.

FIGURE 3 ROC Curves for the Association of Independent Predictors of New-Onset AF



Left atrial (LA) parameters at baseline **(A)** and at 6-month follow-up **(B),** and their change (Δ) from baseline to 6 months after CRT **(C)**. Left atrial volume index (LAVI), LA systolic strain (Ss), LA late diastolic strain (Sa) at 6 months, ΔLAVI, ΔLA Ss and ΔLA Sa had the highest accuracy to predict new-onset atrial fibrillation (AF) with largest areas under the curves (AUC). CI = confidence interval; ESV = end-systolic volume; MR = mitral regurgitation; NS = not significant; ROC = receiver-operating characteristic; other abbreviations as in Figure 2.

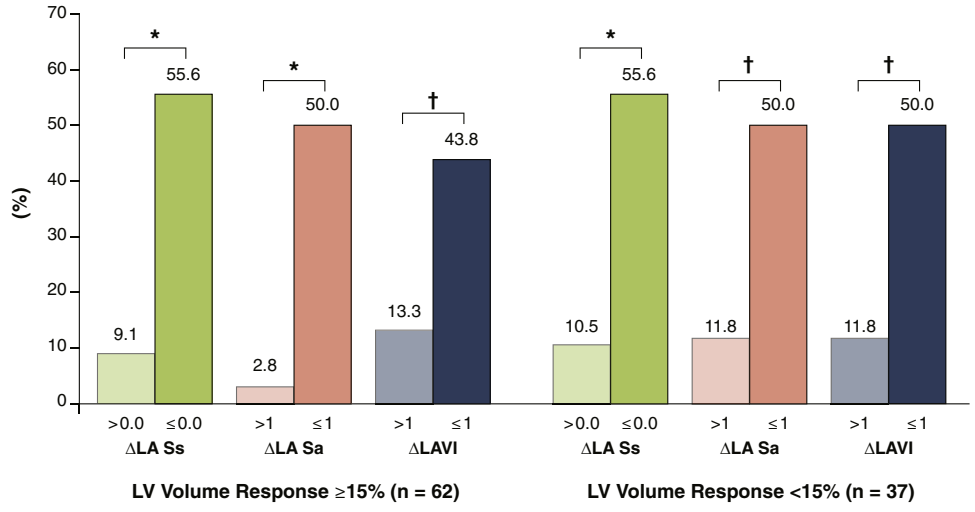
deterioration of the beneficial effects of CRT on these variables (Figure 7).

DISCUSSION

The principal findings of the current study are as follows: 1) LA functional improvement is essential for AF-free survival after CRT and predicts AF-free survival independently from LV volume response; 2) the improvement in LA Ss and Sa strain as a means of LA mechanical reserve also predicts long-term event-free survival after CRT independently from LV volume response and new-onset AF; and 3) new-onset AF is associated with gradual deterioration of the beneficial effects of CRT on LV volumes, EF, and MR over time.

LA FUNCTION AND REVERSE REMODELING. Previous studies explored the effect of CRT on LA reverse remodeling (12,15) and on new-onset AF separately, with inconsistent results regarding the effect of CRT on the development of new-onset AF (5–9). In a substudy of the MADIT-CRT trial, CRT resulted in fewer intermittent atrial tachyarrhythmias, and the investigators showed a significant relationship between

FIGURE 4 New AF in Relation to LV Volume Response and LA Mechanical Changes



Left atrial (LA) mechanical improvement is associated with less frequent new-onset atrial fibrillation (AF) irrespective of left ventricular (LV) volume response (*$p < 0.01$, †$p < 0.05$). Abbreviations as in Figure 3.

LA reverse remodeling and the risk of subsequent atrial tachyarrhythmias (5).

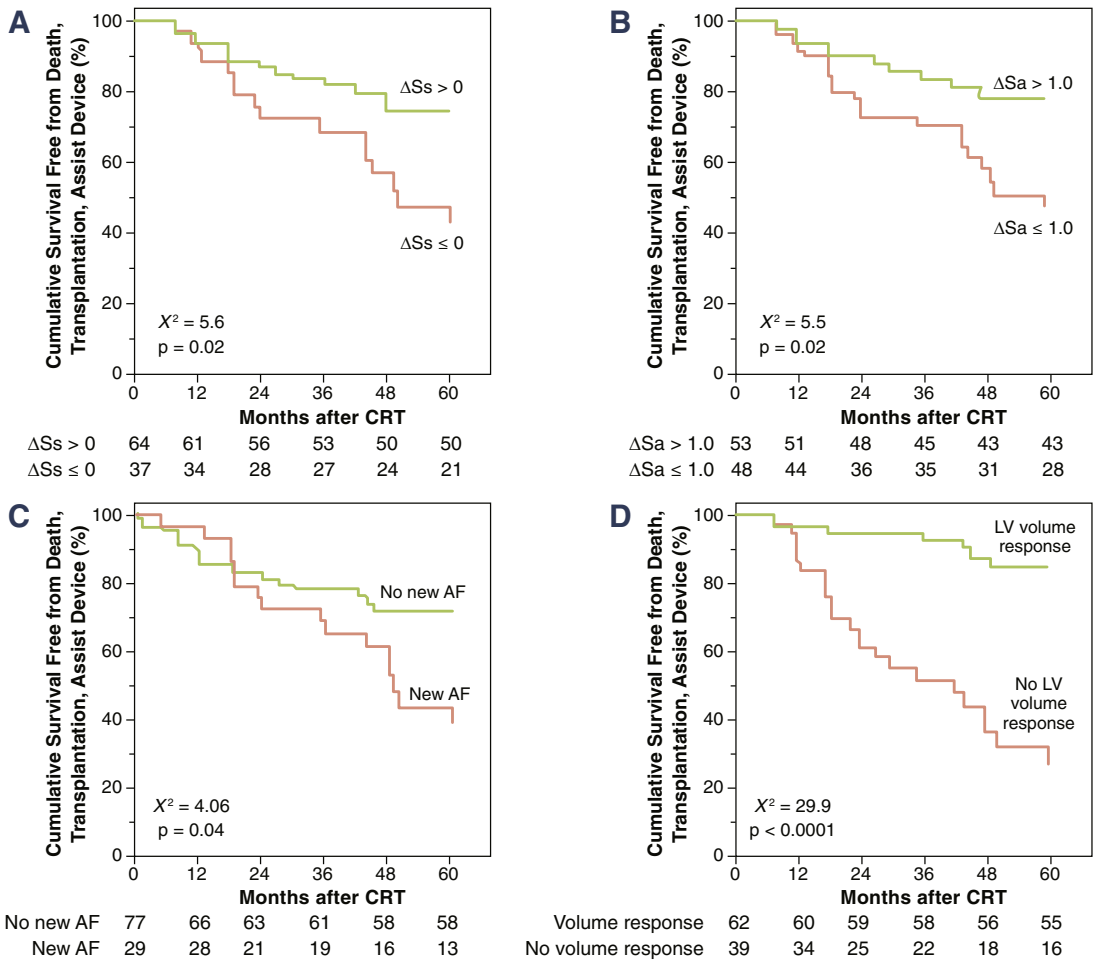
In contrast, in a substudy of the CARE-HF (Cardiac Resynchronization in Heart Failure) trial, no reduction in the incidence of AF was observed after CRT as compared with pharmacological therapy alone; however, AF development was not explored in terms of atrial function or reverse remodeling (9). AF develops in more advanced stages of myocardial disease as evidenced by less atrial deformation and reverse remodeling and poor LV volume response; however, atrial mechanical improvement dominates

TABLE 4 Multivariate Cox Regression Analysis to Identify Independent Predictors of Event-Free Survival Using Baseline, 6-Month, and 6-Month Change Data*

	Model 1		Model 2	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Baseline LA Ss, %	–	–	Not included	–
Baseline LA Sa, %	Not included	–	–	–
Baseline LAVI, ml/m^2	1.05 (1.02–1.09)	0.002	1.05 (1.02–1.09)	0.0001
Baseline ESVI, ml/m^2	–	–	–	–
New-onset atrial fibrillation	–	–	–	–
6 months LA Ss, %	0.93 (0.87–0.99)	0.02	Not included	–
6 months LA Sa, %	Not included	–	0.86 (0.79–0.94)	0.001
6 months LAVI, ml/m^2	–	–	–	–
6 months ESVI, ml/m^2	1.01 (1.00–1.02)	0.015	1.02 (1.01–1.03)	0.0001
New-onset atrial fibrillation	–	–	–	–
Δ LA Ss, %	0.93 (0.852–0.999)	0.04	Not included	–
ΔLA Sa, %	Not included	–	0.86 (0.767–0.970)	0.014
Δ LAVI, (ml/m^2)	–	–	–	–
Δ LV volume, %	0.95 (0.922–0.971)	0.0001	0.94 (0.914–0.966)	0.0001
New-onset atrial fibrillation	–	–	–	–

*In multivariate models, ΔLA Ss and ΔLA Ss are evaluated separately to avoid multicolinearity.
Abbreviations as in Tables 2 and 3.

FIGURE 5 Kaplan-Meier Survival Plots of Probability of Death, Transplantation, and Assist Device-Free Survival After CRT



During follow-up, event-free survival was 78% versus 56% in relation to change in left atrial systolic strain (ΔLA Ss) **(A),** 81% versus 58% in relation to ΔLA late diastolic strain (Sa) **(B),** 75% versus 44% in relation to new atrial fibrillation (AF) **(C),** and 88% versus 41% in relation to left ventricular (LV) volume response **(D)**. CRT = cardiac resynchronization therapy.

over LV volume response for AF-free survival. In fact, LA reverse remodeling is one of the most important pathophysiological mechanisms for the reduction of AF burden, new-onset AF, or atrial tachyarrhythmias (5,6,16).

Several mechanisms can be postulated regarding LA functional improvement in patients who have undergone CRT: the left atrium is exposed to LV pressure during ventricular diastole. With increased LV stiffness, LA pressure rises to maintain adequate LV filling, and the increased atrial wall tension leads to chamber dilation and stretch of the atrial myocardium. With progression of LV dysfunction, LA pump function decreases as a result of increased afterload imposed on the LA myocardium (17). CRT has the potential to induce LV reverse remodeling and to decrease LV wall stress, filling pressure, and MR (18,19). These changes are expected to translate into a decrease in LA wall stretch, reverse remodeling, and an increase in LA contractility. In fact, changes in LA volume and strain in the present study were associated with changes in MR, E/E′ and LV reverse remodeling.

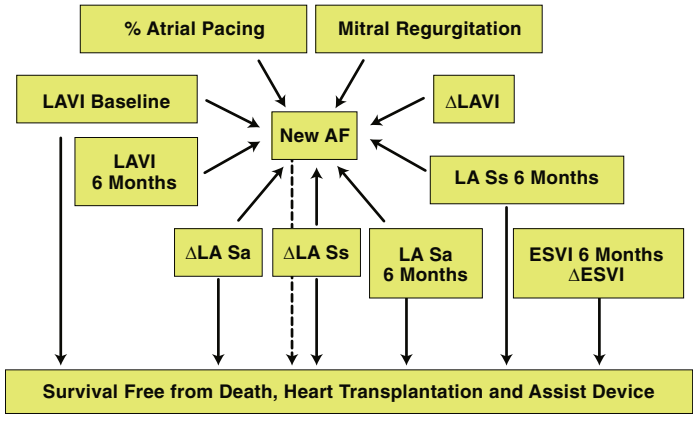
Meanwhile these favorable effects can be realized in relation to the extent of LA afterload mismatch. Improvement in LA function cannot be expected with extensive LA intrinsic disease and fibrosis, which are key factors in the electrophysiological remodeling of the left atrium (20). It is also known that atrial fibroblasts possess more abundant AT1

receptors and display more potent fibrotic response to various stimuli than do ventricles (21). Thus LA reverse remodeling is not observed exclusively in LV volume responders (15). Fung et al. (22) showed that the improvement in LA active emptying fraction after CRT was associated with a reduction in new-onset AF, irrespective of LV reverse remodeling.

The present study provides insights from LA strain for new-onset AF. Previous data regarding the relationship between CRT and the development of AF relied mostly on volume assessments (5,16,23). Although reverse remodeling may not be expected in extremely dilated atria (15), strain is likely to be a more straightforward marker of structural changes, contraction capability, and residual recruitable function regardless of LA size because impairment of LA longitudinal strain was shown to correlate strongly with the extent of LA fibrosis (24). LA strain was also shown to be important for the maintenance of sinus rhythm after cardioversion (25). Therefore strain can strongly and directly predict the propensity to AF (24). In fact, we observed that the favorable effect of improving LA strain on the risk of new AF development persisted after adjustment for changes in LV and LA volumes. Previous attempts to relate AF to LV volume response after CRT oversimplify the underlying mechanical conditions. The percentage of atrial pacing also independently predicted AF development, an observation supporting previous findings that atrial sensing is associated with favorable hemodynamic performance and better atrial contractility (26). Our data have clinical implications to differentiate patients who are expected to derive atrial antiarrhythmic effect from those who are at high risk of developing AF, thus necessitating more aggressive measures or additional therapies addressing AF such as atrioventricular node ablation.

IMPLICATIONS OF ATRIAL MECHANICAL RESERVE AND ATRIAL FIBRILLATION ON OUTCOME. We also found that LA mechanical reserve, defined by LA Ss and Sa at 6 months and the change from baseline to 6 months, was a strong predictor not only of AF development but also of adverse events, independently from new-onset AF and LV and LA volumes. Again in a previous study, LA EF was found to be a predictor of survival after CRT; however, the independent value from other potential confounders was not assessed (6). LA function was also found to be a more robust marker of cardiovascular events than LA size in other patient populations (27,28).

FIGURE 6 Independent Predictors of New-Onset AF and Event-Free Survival After CRT

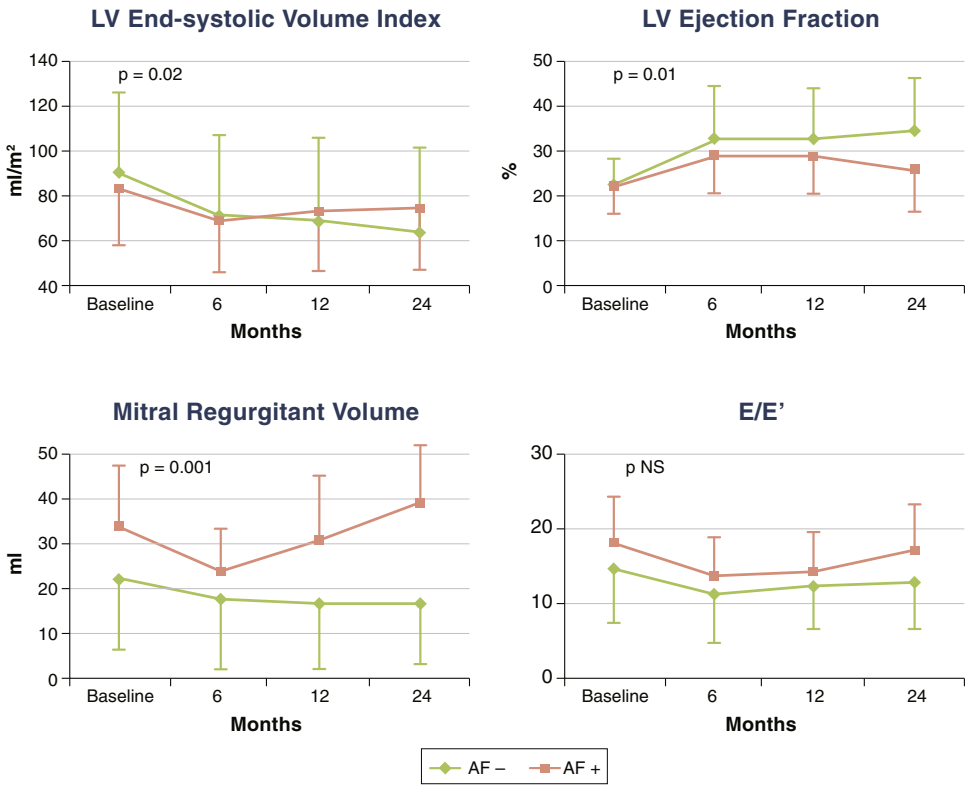


Left atrial (LA) strain, volume, baseline mitral regurgitation, and atrial pacing independently predict new atrial fibrillation (AF) after cardiac resynchronization therapy (CRT). Note that left ventricular volume response to CRT is a strong predictor of event-free survival but is not an independent predictor of new-onset AF, and AF is a univariate but not independent predictor of event-free survival. Δ = change from baseline to 6 months after CRT; ESVI = end-systolic volume index; other abbreviations as Figure 3.

The development of AF is known to exacerbate heart failure symptoms and adversely affect outcomes (29). In accordance, we observed that the development of AF was associated with a gradual deterioration of the beneficial effects of CRT on LV volumes, EF, and MR volume over time. Although the overall outcome after CRT was worse in patients with new-onset AF, the impact of this on survival vanished beside LA strain and LV volume response in multivariate analyses.

STUDY LIMITATIONS. We cannot provide data related to paroxysmal AF episodes before implantation. Previous paroxysmal AF can potentially be associated with some LA functional impairment. However, most of the LA parameters were comparable between the groups at baseline and improved only in patients who remained free of new AF. Therefore, this limitation is unlikely to detract from the implications of our findings that patients with improving atrial function have better AF-free survival after CRT. The results of our multivariable analyses should be interpreted cautiously in view of the relatively small sample size. Strain is influenced by loading conditions. Therefore, we paid attention to tailor the evidence-based treatment of heart failure with maximal tolerated drug doses and included patients in stable clinical condition. We did not use 3D imaging. Although 3D imaging offers accurate volumetric

FIGURE 7 Effect of AF at Corresponding Timing of Follow-Up



Atrial fibrillation (AF) is associated with gradual deterioration of left ventricular (LV) end-systolic volume index, ejection fraction, and mitral regurgitation. E/E′ = ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity.

data, 3D deformation analyses are not readily available for clinical use.

CONCLUSIONS

CRT has favorable effects on LA size, reservoir, and contractile function. Although baseline MR, percentage of atrial pacing, and improvement at 6 months in LAVI, LA compliance, and contractile function as assessed by 2D strain are independent predictors of new AF development, the latter 2 are the most robust indicators of AF-free survival irrespective of LV reverse remodeling and are also independent predictors of long-term outcome.

ACKNOWLEDGMENT The authors are thankful to Hilal Kuzay for her assistance in the pacemaker clinic.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: LA compliance and contractile function can be readily assessed by speckle tracking strain. LA reverse remodeling and improvements in LA compliance and contractile function are necessary for AF-free survival after CRT. LA Ss and Sa are predictors of AF-free survival irrespective of LV reverse remodeling and are also important for long-term outcome.

TRANSLATIONAL OUTLOOK: Further validation of the present data in patients who have had CRT will provide important clinical implications to differentiate patients who are expected to derive atrial antiarrhythmic effect from those who are at high risk of developing AF, thus necessitating more aggressive measures or additional therapies addressing AF, such as atrioventricular node ablation.

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KEY WORDS atrial fibrillation, cardiac resynchronization therapy, echocardiography