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ORIGINAL INVESTIGATIONS

Restoring Sinus Rhythm Reverses Cardiac Remodeling and Reduces Valvular Regurgitation in Patients With Atrial Fibrillation

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ABSTRACT

BACKGROUND Cardiac chamber remodeling in atrial fibrillation (AF) reflects the progression of cardiac rhythm and may affect functional regurgitation.

OBJECTIVES The purpose of this study was to explore the 3-dimensional echocardiographic variables of cardiac cavity remodeling and the impact on functional regurgitation in patients with AF with/without sinus rhythm restoration at 12 months.

METHODS A total of 117 consecutive patients hospitalized for AF were examined using serial 3-dimensional transthoracic echocardiography at admission, at 6 months, and at 12 months (337 examinations).

RESULTS During follow-up, 47 patients with active restoration of sinus rhythm (SR) (through cardioversion and/or ablation) had a decrease in all atrial indexed volumes (Vi), end-systolic (ES) right ventricular (RV) Vi, an increase in end-diastolic (ED) left ventricular Vi, and an improvement in 4-chambers function ($P < 0.05$). Patients with absence/failure of restoration of SR (n = 39) had an increase in ED left atrial Vi and ED/ES RV Vi without modification of 4-chambers function, except for a decrease in left atrial emptying fraction ($P < 0.05$). Patients with spontaneous restoration of SR (n = 31) had no changes in Vi or function. The authors found an improvement vs baseline in severity of functional regurgitation in patients with active restoration of SR (tricuspid and mitral regurgitation) and in spontaneous restoration of SR (tricuspid regurgitation) ($P < 0.05$). In multivariable analysis, right atrial and/or left atrial reverse remodeling exclusively correlated with intervention (cardioversion and/or ablation) during 12-month follow-up.

CONCLUSIONS Management of AF should focus on restoration of SR to induce anatomical (all atrial Vi, ES RV Vi) and/or functional (4 chambers) cardiac cavity reverse remodeling and reduce severity of functional regurgitation. (Thromboembolic and Bleeding Risk Stratification in Patients With Non-valvular Atrial Fibrillation [FASTRHAC]; NCT02741349) (J Am Coll Cardiol 2022;79:951-961) © 2022 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

3D = 3-dimensional
AF = atrial fibrillation
ED = end-diastole
ES = end-systole
i = indexed
LAV = left atrial volume
LVV = left ventricular volume
RAV = right atrial volume
RVV = right ventricular volume
SR = sinus rhythm

The recent European Society of Cardiology guidelines[1] and the European Association of Cardiovascular Imaging/European Heart Rhythm Association expert consensus document[2] both highlighted the importance of imaging to evaluate the atrial fibrillation (AF) substrate. Atrial remodeling is defined as a change in atrial structure or function that promotes atrial arrhythmias.[3] The close interaction between atrial myopathy, AF, and stroke involves multiple determinants such as aging, inflammation, oxidative stress, fibrosis, and electrical and autonomic remodeling.[4] These interactions create a vicious cycle between worsening of atrial myopathy and increased risk of sustained AF and stroke.[4,5]

SEE PAGE 962

In AF, most of the literature on heart remodeling has focused on the left atrium (LA),[6] with only limited data on the left ventricle (LV), right atrium (RA), and right ventricle (RV). The aims of this analysis, using data from the FASTRHAC (Thromboembolic and Bleeding Risk Stratification in Patients with Nonvalvular Atrial Fibrillation) study, were to evaluate the anatomical and functional changes that occur in all cardiac chambers in AF using 3-dimensional (3D) echocardiography at 12-month follow-up and, thus, to evaluate the impact on functional regurgitation.

METHODS

STUDY POPULATION, DESIGN, DEFINITION OF ATRIAL REMODELING. FASTRHAC is a national, multicenter, prospective French study of patients hospitalized for AF (Ethics committee authorization: CPP Ile de France V, number: 2014-A00280-47; NCT02741349). The FASTRHAC methods have been previously published.[7]

All consecutive patients (age ≥18 years) hospitalized for paroxysmal or persistent AF diagnosed on a 12-lead electrocardiogram who provided written informed consent were included. Exclusion criteria were organic valvular disease defined according to the guidelines,[8-10] presence of a mechanical or biological prosthesis, contraindication to anticoagulant treatment, lack of affiliation to a social security regimen, severe psychiatric history, and subjects considered unlikely to present for follow-up. Comprehensive clinical characteristics, biological variables, and 2-dimensional (2D)/3D transthoracic and transesophageal echocardiography data were collected over 2 years. CHA_2DS_2-VASc score was collected in each patient. This analysis focuses on the first year of follow-up in 117 consecutive patients enrolled in the study.

Three groups were defined according to the type of management for AF and the cardiac rhythm at 12 months (**Figure 1**): the AF group comprised patients with persistence of AF at 12 months; the active sinus rhythm (SR) group comprised patients who underwent successful cardioversion and/or ablation and were in SR at 12 months; and the spontaneous SR group comprised patients with spontaneous restoration of SR <24 hours after hospitalization and who were in SR at 12 months. For the AF group, the cardiac rhythm was AF at each echocardiography evaluation during follow-up. For the active SR, the cardiac rhythm was AF at admission and SR at 6-month and 12-month follow-up. For the spontaneous SR, the cardiac rhythm was SR at each echocardiography evaluation during follow-up.

RA and/or LA reverse remodeling was defined as a ≥15% reduction in end-systolic (ES) volume in at least 1 of the 2 atria.[11]

TRANSTHORACIC ECHOCARDIOGRAPHY. Transthoracic echocardiography was performed within 24 hours of admission by experienced cardiologists using an X5-1 transducer on an IE 33 system or an X5-1 transducer on EPIQ 7 and CVx (Philips Medical Systems). Examinations were performed at admission and at 6 and 12 months. The data were transferred and analyzed offline using a TOMTEC workstation (Image Arena, TOMTEC) (L.S.D., I.K., and E.C.).

The 2D and 3D measurements were analyzed following U.S. and European Chamber Quantitation Guidelines.[12,13] Volumetric measurements were indexed (i) to body surface area and performed at ES and end-diastole (ED). Functional atrioventricular regurgitations were evaluated using the largest 2-dimensional vena contracta at admission and during follow-up.[9,10] Measurement of the vena contracta

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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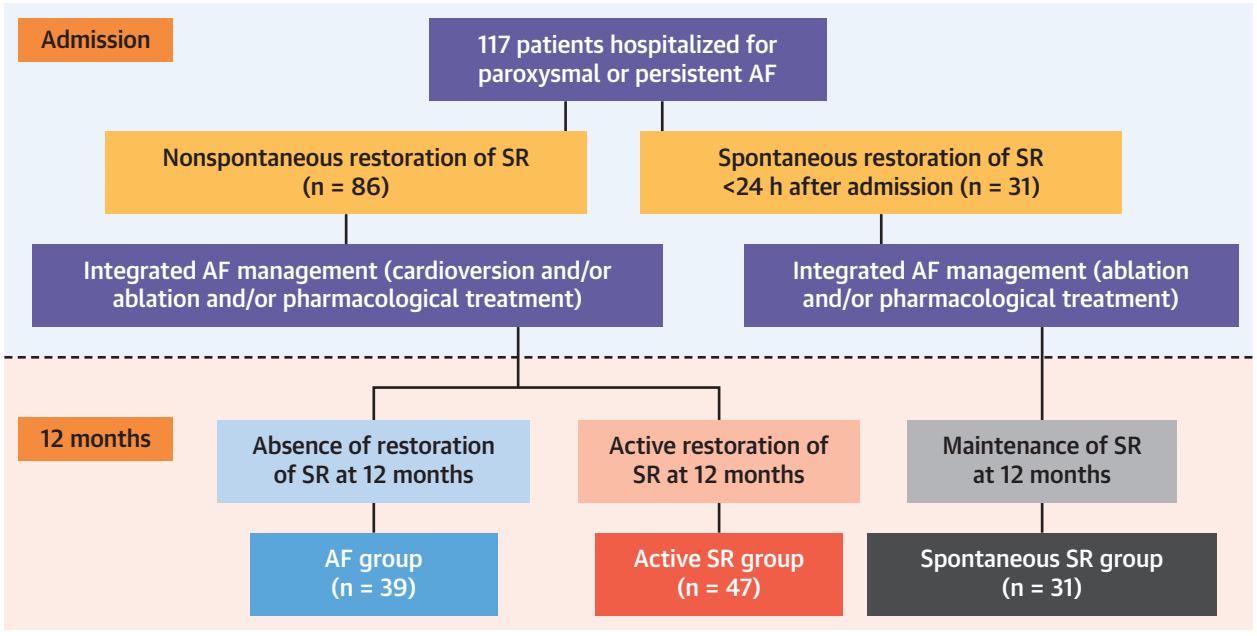
FIGURE 1 Flow Chart of Patients Hospitalized for Paroxysmal or Persistent AF



Definition at 1 year in the AF, active SR, and spontaneous SR groups. AF = atrial fibrillation; SR = sinus rhythm.

of mitral regurgitation was done in a parasternal long-axis zoomed view and of the vena contracta of tricuspid regurgitation in apical 4-chamber zoomed view.[10] 3D datasets were deemed adequate for analysis if all cavity segments were visible in the dynamic data set. The high-volume rate mode was used in all the patients to avoid stitching artefacts, to maintain an adequate volume rate, and to allow an average based on 2 cardiac cycles. 3D full-volume datasets were analyzed using software specifically designed for 3D volumetric analysis of the RA, RV, LA, and LV (4D LV/LA analysis and 4D RV function software).

3D atrial analysis measured 3D ES and ED right atrial volume (RAV) and left atrial volume (LAV). 3D ventricular analysis evaluated 3D ES and ED right ventricular volumes (RVV) and left ventricular volumes (LVV). Using these data, the following indexes were calculated:

3D right atrial emptying fraction
= (3D ES RAV − 3D ED RAV)/(3D ES RAV)
3D right ventricular ejection fraction
= (3D ED RVV − 3D ES RVV)/(3D ED RVV)
3D left atrial emptying fraction
= (3D ES LAV− 3D ED LAV)/(3D ES LAV)
3D left ventricular ejection fraction
= (3D ED LVV − 3D ES LVV)/(3D ED LVV)

STATISTICAL ANALYSIS. Continuous variables were compared using the nonparametric Kruskal-Wallis rank test at baseline and at 6-month and 12-month follow-up. Categorical variables were compared using the chi-square or Fisher exact test. To compare remodeling of the 4 cardiac chambers over time, the echocardiographic parameters were compared using the Wilcoxon signed-rank test for matched samples. Logistic regression analyses were performed to identify variables associated with atrial reverse modeling at 12 months. All variables with $P < 0.10$ in univariate analyses were entered into the multivariable model. All analyses were performed using STATA version 12 (StataCorp). A value of $P < 0.05$ was considered statistically significant. The P values and 95% CIs presented in this report have not been adjusted for multiplicity; therefore, inferences drawn from these statistics may not be reproducible.

RESULTS

CLINICAL AND BIOLOGICAL CHARACTERISTICS, AND ECHOCARDIOGRAPHY AT ADMISSION. At 12 months, 39 (33.3%) patients were in the AF group, 47 (40.2%) in the active SR group, and 31 (26.5%) in the spontaneous SR group (Figure 1). The clinical

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TABLE 1 Baseline Characteristics According to Cardiac Rhythm Status at 1-Year Follow-Up

	AF (n = 39)	Active SR (n = 47)	Spontaneous SR (n = 31)	*P* Value
Cardiovascular risk factors				
Male	25 (64.1)	31 (66.0)	16 (51.6)	0.41
Age, y	68.5 ± 12.2	64.1 ± 11.6	62.8 ± 14.5	0.10
Body mass index, kg/m^2	26.6 (23.6-31.2)	26.4 (23.9-30.9)	24.0 (21.8-29.6)	0.13
Hypertension	25 (64.1)	18 (38.3)[a]	19 (61.3)[b]	0.032
Diabetes	11 (28.2)	6 (12.8)	3 (9.7)	0.073
Dyslipidemia	13 (33.3)	16 (34.0)	13 (41.9)	0.71
Current smoker	6 (15.4)	12 (25.5)	6 (19.4)	0.50
Alcohol consumption[c]	10 (25.6)	14 (28.8)	5 (16.1)	0.39
Medical history				
Myocardial infarction	12 (64.1)	15 (31.9)[a]	3 (9.7)[d]	0.021
Heart failure	13 (33.3)	4 (8.5)[a]	1 (3.2)[d]	0.001
Stroke	4 (10.3)	3 (6.4)	1 (3.2)	0.51
Pulmonary embolism	3 (7.7)	1 (2.1)	1 (3.2)	0.52
Chronic obstructive pulmonary disease	5 (12.8)	1 (2.1)	0 (0.0)	0.031
Renal insufficiency	7 (18.0)	1 (2.1)	0 (0.0)[d]	0.003
Cancer	6 (15.4)	5 (10.6)	5 (18.1)	0.73
Obstructive sleep apnea syndrome	5 (12.8)	2 (4.3)	1 (3.2)	0.27
CHA_2DS_2-VASc score				
0	2 (5.1)	5 (10.6)	3 (9.7)	0.19
1	2 (5.1)	6 (12.8)	7 (22.6)	
≥2	35 (89.7)	36 (76.6)	21 (67.7)	
First diagnosis of AF	14 (35.9)	32 (68)[a]	27 (87)[d]	<0.0001
AF classification				
Paroxysmal	10 (26.0)	17 (36.2)	31 (100.0)[b,d]	<0.0001
Persistent	29 (74.0)	30 (63.8)	0 (0.0)	
Reason for hospitalization				<0.0001
Isolated AF	22 (56.4)	25 (53.2)	28 (90.3)[b,d]	
AF + heart failure	14 (35.9)	21 (44.7)	0 (0.0)	
AF + hypokalemia, syncope, or constrictive pericarditis	3 (7.7)	1 (2.1)	3 (9.7)	
AF management during the first year				
No intervention	18 (46.2)	0 (0.0)[a]	21 (67.7)[b]	<0.0001
Intervention (cardioversion and/or ablation)	21 (53.9)	47 (100.0)	10 (32.3)	
Biological variables				
High-sensitivity C-reactive protein, mg/L (n = 36/44/31)	3.0 (0.9-8.4)	3.3 (2.2-7.6)	1.1 (0.6-3.1)[b,d]	0.0059
Hemoglobin A1C, % (n = 37/44/30)	6.0 (5.7-6.3)	5.8 (5.5-6.3)	5.5 (5.1-5.7)[b,d]	0.0008
Glomerular filtration rate, mL/min/1.73 m^2 (MDRD)	67 (49-79)	71 (66-83)	82 (65-99)[d]	0.0090
B-type natriuretic peptide, pg/mL (n = 39/47/30)	298 (190-424)	252 (103-506)	90 (45-186)[b,d]	0.0001
Troponin, ng/L (n = 39/47/29)	0.04 (0.04-0.04)	0.04 (0.04-0.04)	0.04 (0.04-0.04)	0.74
D-dimer, ng/mL (n = 36/44/30)	330 (270-492)	360 (270-730)	272 (270-410)	0.20
3D echocardiography				
Cardiac rhythm during the echocardiography at admission	AF	AF	SR	-

Continued on the next page

characteristics of the population according to cardiac rhythm at 12 months are shown in **Table 1.** A total of 72 (61.5%) patients were men, and the mean age was 65.2 ± 12.7 years. The active SR group had a lower prevalence of hypertension compared with the other groups. History of myocardial infarction, heart failure, chronic obstructive pulmonary disease, and renal insufficiency were more prevalent in the AF group. There were no significant differences between groups in the CHA_2DS_2-VASc score. At admission, 73 (62.4%) patients were considered as having a first diagnosis of AF, predominantly in the active SR and spontaneous SR groups. AF pattern at admission differed between groups. The reason for hospitalization was more frequently isolated AF in the spontaneous SR group, whereas AF with heart failure was more frequent in the other groups. The spontaneous SR group had lower values for high-sensitivity C-reactive protein, hemoglobin A1C, and B-type natriuretic peptide, and a higher glomerular filtration rate. There were no

TABLE 1 Continued

	AF (n = 39)	Active SR (n = 47)	Spontaneous SR (n = 31)	*P* Value
3D volume rate: average of the 3D volume rate of the 4 cavities, Hz	19 (18-20)	18 (17-20)	19 (18-21)	0.2152
Right atrium				
3D ED RAVi, mL/m^2 (n = 34/41/29)	26.0 (21.5-30.7)	22.6 (17.3-34.3)	16.0 (13.9-20.7)[b,d]	0.0001
3D ES RAVi, mL/m^2 (n = 34/41/29)	34.9 (30.4-42.3)	31.3 (25.0-42.1)	29.0 (22.0-33.5)[d]	0.013
3D RA EmF, % (n = 34/41/29)	24.4 (21.1-29.3)	25.4 (20.2-36.4)	42.5 (33.9-46.4)[b,d]	0.0001
Right ventricle				
3D ED RVVi, mL/m^2 (n = 33/38/29)	53.2 (51.4-72.5)	60.6 (50.9-71.4)	68.7 (58.9-80.5)[b,d]	0.0094
3D ES RVVi, mL/m^2 (n = 33/38/29)	36.9 (31.6-47.8)	42.5 (32.3-51.1)	36.2 (32.1-45.6)	0.48
3D RVEF, % (n = 33/38/29)	31.5 (26.9-36.9)	31.6 (25.4-37.2)	44.1 (40.4-50.4)[b,d]	0.0001
Left atrium				
3D ED LAVi, mL/m^2 (n = 35/41/29)	32.3 (24.8-40.7)	31.7 (25.6-39.7)	19.7 (17.3-24.7)[b,d]	0.0001
3D ES LAVi, mL/m^2 (n = 35/41/29)	43.7 (36.1-50.9)	41.7 (35.4-48.5)	35.8 (30.4-44.9)[d]	0.0094
3D LA EmF, % (n = 35/41/29)	29.3 (25.8-32.1)	24.7 (19.6-30.9)[a]	42.6 (36.8-46.8)[b,d]	0.0001
Left ventricle				
3D ED LVVi, mL/m^2 (n = 35/41/29)	53.3 (43.6-60.8)	50.6 (37.5-64.2)	56.0 (51.0-65.1)	0.16
3D ES LVVi, mL/m^2 (n = 35/41/29)	29.8 (23.1-38.6)	28.0 (22.7-40.2)	24.7 (23.2-27.2)[d]	0.17
3D LVEF, % (n = 35/41/29)	41.7 (36.7-50.8)	38.0 (30.0-47.5)	55.2 (52.2-56.9)[b,d]	0.0001

Values are n (%), mean ± SD, or median (IQR). [a]$P < 0.05$ between AF group and active SR group. [b]$P < 0.05$ between active SR group and spontaneous SR group. [c]Defined as more than 2 glasses of wine per day or equivalent. [d]$P < 0.05$ between AF group and spontaneous SR group. No corrections for multiple testing were applied.

3D = 3-dimensional; AF = atrial fibrillation; ED = ventricular end-diastole; EmF = emptying fraction; ES = ventricular end-systole; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; MDRD = Modification of Diet in Renal Disease; RA = right atrium; RV = right ventricle; SR = sinus rhythm; Vi = indexed volumes.

significant differences regarding troponin and D-dimer concentrations.

The spontaneous SR group had lower values for 3D atrial indexed volume (ED/ES right atrial indexed volume [RAVi] and left atrial indexed volume [LAVi]) and higher 3D ED RVVi values, with better 3D function of the cavities (RA emptying fraction, RV ejection fraction, LA emptying fraction, and LV ejection fraction). With the exception of 3D LA emptying fraction, the characteristics of the active SR group did not differ from those of the AF group. There were no significant differences in 3D ES RVVi or ED/ES LVVi between the 3 groups (**Table 1**).

Overall, the 2D cavity volumes and functions at admission were similar to the 3D results. The active SR group had greater mitral regurgitation vena contracta ($P = 0.01$). The spontaneous SR group had a lower median pulmonary arterial pressure vs the AF group ($P < 0.05$). There were no statistically significant differences between groups with regard to tricuspid regurgitation and aortic regurgitation vena contracta (Supplemental Table 1).

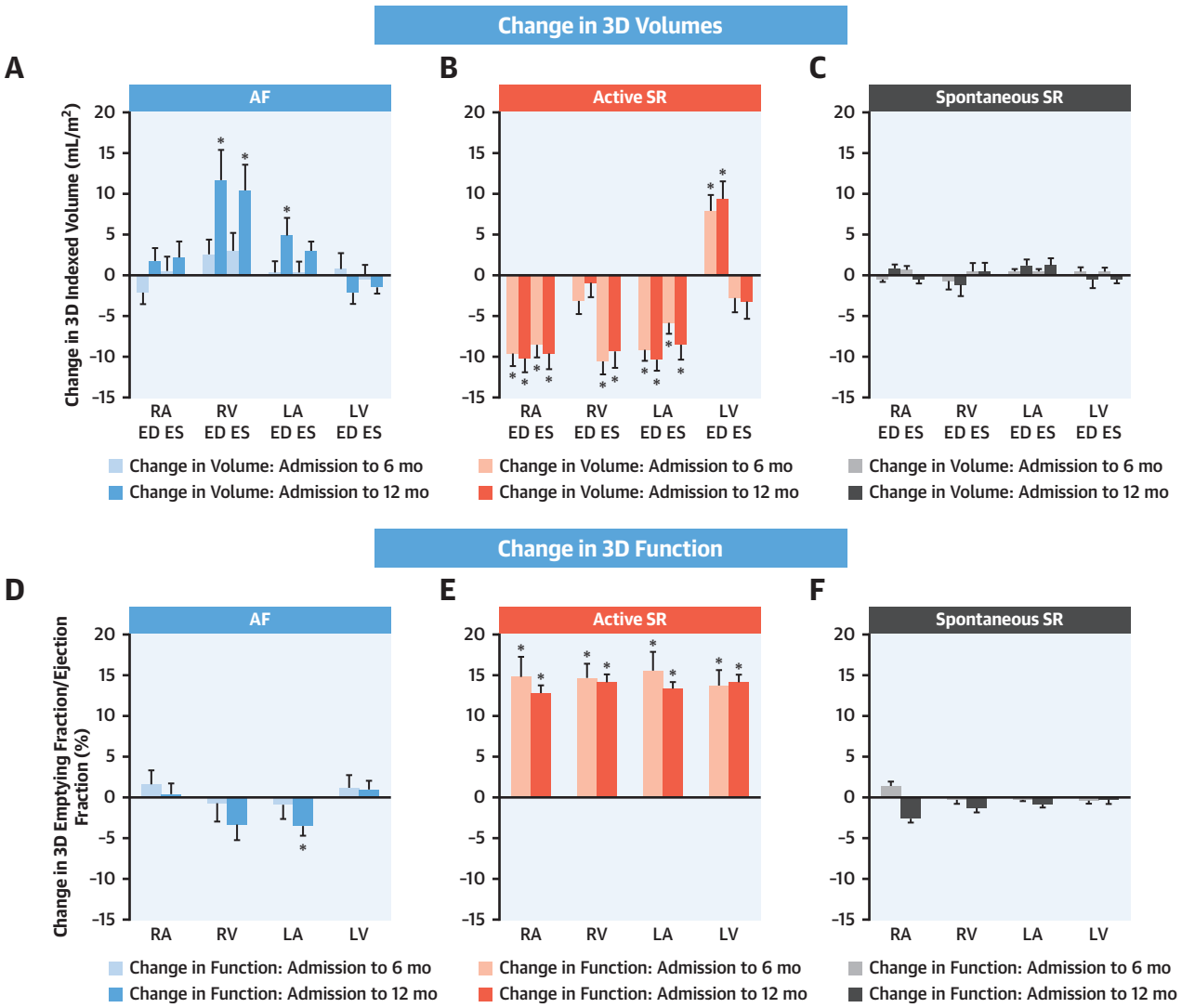
CHANGE IN ECHOCARDIOGRAPHIC VARIABLES DURING 1-YEAR FOLLOW-UP. A total of 117 patients underwent echocardiography at admission, 103 patients at 6 months, and 117 patients at 12 months (a total of 337 examinations). Offline analysis in 3D echocardiography was feasible in 286 (84.9%) examinations. Changes in 3D volumes and function during follow-up are displayed in **Figure 2** and Supplemental Table 2, changes in 2-dimensional echocardiographic measurements in Supplemental Table 3, and changes in tricuspid regurgitation and mitral regurgitation vena contracta in **Figure 3**. There were no significant differences in the volume rate of the 3D images between groups at the time of each follow-up (Supplemental Table 2).

CHANGE IN 3D VOLUMES BETWEEN BASELINE AND FOLLOW-UP. In the AF group, there were no differences in 3D indexed volumes during follow-up except for an increase in ED/ES RVVi and ED LAVi (**Figure 2A**). In the active SR group, there were decreases in all atrial indexed volumes (3D ED/ES RAVi and LAVi) and 3D ES RVVi associated with an increase in 3D ED LVVi (**Figure 2B**). There were no significant differences in 3D indexed volumes in the spontaneous SR group over time (**Figure 2C**).

CHANGE IN 3D CARDIAC FUNCTION BETWEEN BASELINE AND FOLLOW-UP. In the AF group, there were no significant changes in 3D function in the 4 chambers during follow-up, except for a decrease in LA emptying fraction (**Figure 2D**). In the active SR group, 3D function improved in all 4 chambers (**Figure 2E**). There were no significant differences in 3D function in the spontaneous SR group (**Figure 2F**).

CHANGE IN 2D ECHOCARDIOGRAPHIC VARIABLES BETWEEN BASELINE AND FOLLOW-UP. Overall, 2D cavity volumes and function showed the same trends

FIGURE 2 Change in 3D Volumes and 3D Function

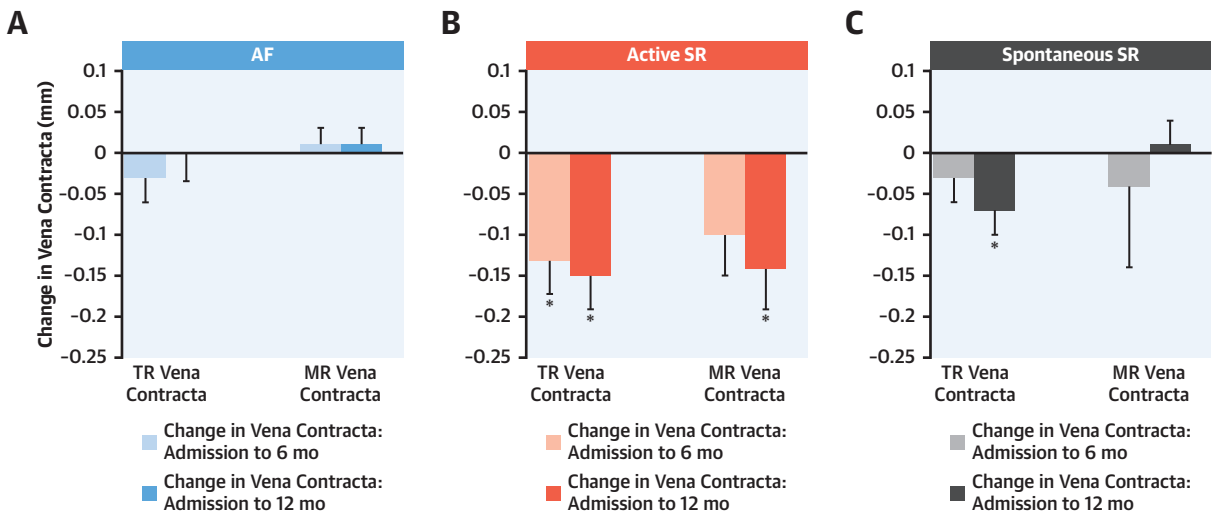


Differences in 3D indexed volumes **(A to C)** and 3D emptying fraction/ejection fraction **(D to F)** between baseline and follow-up in the AF, active SR, and spontaneous SR groups. A positive value represents an increase and a negative value a decrease in the 3D volume/3D function during follow-up. *$P < 0.01$, comparison of 3D volume with baseline (admission vs 6 months or admission vs 12 months) with Wilcoxon matched-pairs signed-ranks test. The **errors bars** are SE of mean. No corrections for multiple testing were applied. 3D = 3-dimensional; AF = atrial fibrillation; ED = end-diastolic; ES = end-systolic; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; SR = sinus rhythm.

as those obtained with 3D echocardiography (Supplemental Table 3). The lowest severity of tricuspid and mitral regurgitation as assessed with vena contracta was found in the active SR group (Supplemental Table 3). Compared with baseline, there were significant improvements in tricuspid and mitral regurgitation when assessed with vena contracta in the active SR group. Similarly, a decrease in tricuspid regurgitation in the spontaneous SR group was also seen (**Figure 3**).

CHANGE IN 3D AND 2D VARIABLES BETWEEN MONTHS 6 AND 12. In the AF group, there was a significant increase between months 6 and 12 in 3D ED RAVi, 3D ES RAVi, 3D ED RVVi, 3D ES RVVi, and 3D ED LAVi, and a decrease in 2D ED LVVi, 2D ES LVVi, and 3D LA emptying fraction. In the active SR group, there was a significant increase in 3D ES LVVi, RV FAC, and PAP, and a decrease in 2D ED RAVi and 2D ES RAVi. There were no significant differences between months 6 and 12 in the spontaneous SR group (Supplemental Tables 2 and 3).

FIGURE 3 Change in Vena Contracta



Differences in tricuspid regurgitation and mitral regurgitation vena contracta between baseline and follow-up in the **(A)** AF, **(B)** active SR, and **(C)** spontaneous SR groups. A positive value represents an increase, and a negative value a decrease in vena contracta during follow-up. *$P < 0.05$, comparison of 2D vena contracta with baseline (admission vs 6 months or admission vs 12 months) with Wilcoxon matched-pairs signed-ranks test. The **errors bars** are SE of mean. No corrections for multiple testing were applied. MR = mitral regurgitation; TR = tricuspid regurgitation; other abbreviations as in Figure 2.

PREDICTORS OF RA AND/OR LA REMODELING DURING 1-YEAR FOLLOW-UP. The characteristics of the population according to RA and/or LA reverse remodeling are shown in Supplemental Table 4. On univariate logistic regression analysis, intervention during the first year of follow-up (cardioversion and/or ablation), higher indexed volume of 3D ED RAVi and LAVi, lower 3D LA emptying fraction, 3D RV ejection fraction, and 3D LV ejection fraction at admission were associated with RA and/or LA reverse remodeling (Table 2). Only intervention during the first year of follow-up (cardioversion and/or ablation) remained significantly associated with reverse remodeling after multivariable adjustment.

DISCUSSION

Our study suggests that anatomical (all atrial Vi, ES RV Vi) and/or functional (4 chambers) reverse cardiac cavity remodeling occurred exclusively in patients with active restoration of SR during 1 year of follow-up. In the AF group at 1 year, both ED/ES RVVi and ED LAVi increased, whereas 3D LA emptying fraction decreased. Interestingly, we found a reduction in severity of tricuspid and mitral regurgitation after active restoration of SR. After multivariable adjustment, cardioversion and/or ablation during the first year of follow-up were the only variables significantly associated with RA and/or LA reverse remodeling.

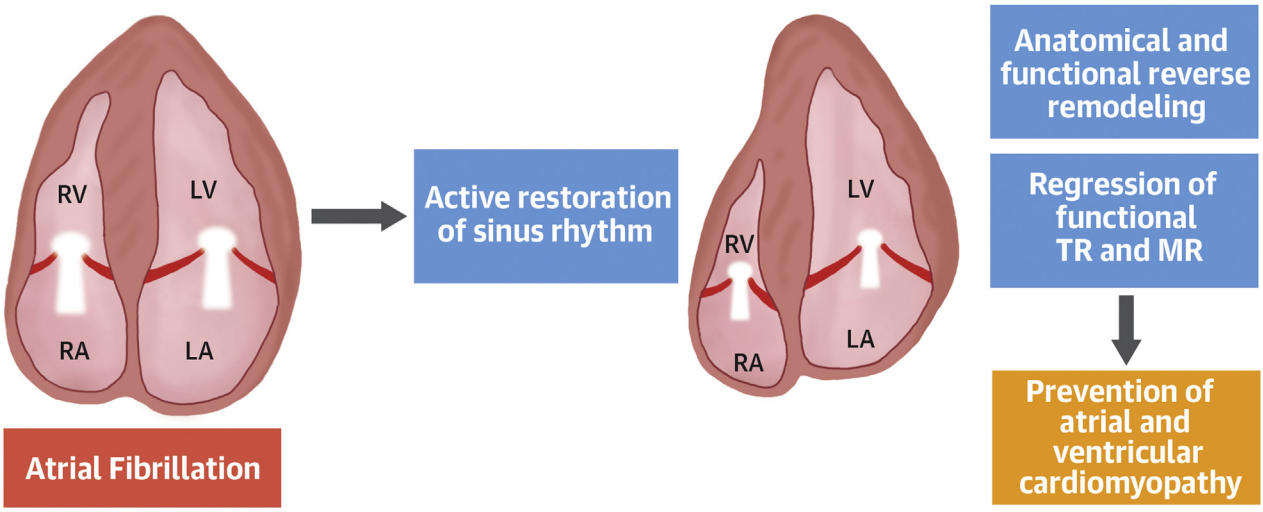
CLINICAL IMPLICATIONS OF CARDIAC CAVITY REMODELING. Multimodality imaging using echocardiography, cardiac magnetic resonance, and computed tomography is the cornerstone for evaluating AF. To date, the LA cavity is the most studied cardiac chamber in AF. In a healthy population,

TABLE 2 Univariate/Multivariable Logistic Regression for Prediction of RA and/or LA Reverse Remodeling During 1-Year Follow-Up

	Univariate Analysis		Multivariable Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Average 3D volume rate of the 4 chambers at admission	0.95 (0.75-1.20)	0.65	—	—
Hospitalization for AF + heart failure (referent: AF alone)	2.37 (0.86-6.55)	0.095	0.83 (0.20-3.49)	0.80
Intervention during first year (cardioversion and/or ablation) (referent: no intervention)	32.63 (4.13-258.01)	0.001	26.93 (3.01-240.93)	0.003
Admission 3D ED RAVi, per 5 mL/m^2 increase	1.26 (1.01-1.58)	0.038	1.04 (0.69-1.57)	0.86
Admission 3D RAEmF, per 5% increase	0.88 (0.71-1.09)	0.24	—	—
Admission 3D RVEF, per 5% increase	0.76 (0.59-0.99)	0.041	0.96 (0.67-1.37)	0.82
Admission 3D ED LAVi, per 5 mL/m^2 increase	1.31 (1.05-1.63)	0.015	1.19 (0.75-1.86)	0.46
Admission 3D LAEmF, per 5% increase	0.62 (0.48-0.82)	0.001	0.80 (0.55-1.18)	0.26
Admission 3D LVEF, per 5% increase	0.78 (0.64-0.96)	0.017	1.00 (0.73-1.38)	0.98

LAEmF = left atrial emptying fraction; LAVi = left atrium volume indexed to body surface area; RAEmF = right atrial emptying fraction; RAVi = right atrium volume indexed to body surface area; RVEF = right ventricular ejection fraction; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION **Reverse Cardiac Remodeling/Improvement of Regurgitation After Restoration of Sinus Rhythm**



Soulat-Dufour, L. et al. J Am Coll Cardiol. 2022;79(10):951-961.

At 1 year of follow-up in atrial fibrillation, active restoration of sinus rhythm induced cardiac anatomical (atrial indexed volume, end-systolic right ventricular indexed volume) and/or functional (4 chambers) reverse remodeling and a regression of functional TR and MR. An active management of atrial fibrillation focused on restoration of sinus rhythm could prevent both atrial and ventricular cardiomyopathy and reduce functional atrioventricular regurgitation. LA = left atrium; LV = left ventricle; MR = mitral regurgitation; RA = right atrium; RV = right ventricle; TR = tricuspid regurgitation.

anatomical and functional evaluation of the LA is useful to identify patients at higher risk of incident AF.[14-21] Moreover, in patients with established AF, anatomical and functional evaluation of the LA is useful to evaluate reverse remodeling after ablation[7,11,22-27] and to stratify risk of stroke.[28-31] However, few data are available regarding the other cardiac chambers. Conversely, some RA[16,21] and RV[32] variables appear correlated with risk of incident AF, whereas a few scattered studies have reported LV, RV,[27] and RA[7,25,26] reverse remodeling after restoration of SR.

To our knowledge, this is the first 3D echocardiography study in AF that found anatomical (atrial Vi, ES RV Vi) and/or functional (4 chambers) reverse remodeling of cardiac cavities after restoration to SR at 1 year of follow-up. Paradoxically, we found an increase in 3D ED LVVi during follow-up that could be correlated with an improvement in LV diastolic function after restoration of SR. It is also interesting to observe that the increase in ED/ES 3D RVVi and 3D ED LAVi, coupled with the decrease in LA emptying fraction in the AF group during follow-up, highlights the negative effect of persistent AF on heart cavity size. Moreover, intervention (cardioversion and/or ablation) in AF during the first year of follow-up was the only independent factor to be significantly associated with RA and/or LA reverse remodeling. Thus, the option of active restoration of SR could be discussed with patients to avoid worsening of both atrial and ventricular dysfunction (**Central Illustration**). Our results are consistent with literature emphasizing the importance of ablation in patients with heart failure and LV dysfunction <35%.[33] Moreover, it is interesting to note that the rates of use of heart failure therapies at 12 months (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, digitalis) were equivalent in the 3 groups, except for a high use of diuretic agents in the AF group (Supplemental Table 5). These results suggest that remodeling in the active SR group was not associated with differences in heart failure therapy.

TRICUSPID AND MITRAL REGURGITATION AFTER RESTORATION OF SR. Our study revealed decreased tricuspid and mitral regurgitation after restoration of

SR in AF. The changes in mitral and tricuspid regurgitations can be correlated with reverse remodeling in the cardiac chambers in the active SR group. The change in the spontaneous SR group could be correlated with the change in intracardiac hemodynamics after restoration of SR. Some studies appear to demonstrate a link between functional regurgitation and AF and their association with a worse prognosis.[34-36] Thus, our data suggest that restoration of SR in AF could interfere with the deleterious nature of functional regurgitation in AF (**Central Illustration**). Further investigations will, however, be necessary to confirm our results.

SPONTANEOUS RESTORATION OF SR. A recent report discussed the role of spontaneous restoration of SR in the management of AF in the emergency department.[37] Scattered data in the literature have established their determinants.[38-40] In our study, spontaneous restoration of SR represents 26.5% of the patients hospitalized for AF in our cohort. This population had specific baseline clinical, biological, and echocardiographic characteristics. Interestingly, in comparison with normal values,[41,42] this group had diminution of atrial function at baseline. Although this could suggest an initial atrial stunning, the persistence of both atrial dysfunction at 12 months appears to be more likely correlated with an underlying atrial disease (ie, atrial cardiomyopathy).[43]

AF SPECIFICITIES: 3D ACQUISITION, HIGH HEART RATE. Limited data are available in the literature and guidelines about the optimal way to perform 3D measurements in AF. We chose to use the high-volume rate mode in AF because it was the best acquisition strategy as it allowed an average based on 2 cycles. The 2015 guidelines[12] suggested the average of 3 beats for patients in normal sinus rhythm and a minimum of 5 beats in patients with AF. The accuracy of our measurements would probably have been improved if the averaging of the measurements could have been performed on a larger number of cycles.

The impact of elevated heart rates on 3D echo volume measurements is not fully understood. In theory, the highest heart rate at admission in the active SR group may have led to underestimation of maximum volumes and overestimation of minimal cavity volumes for any given cavity. However, the potential confounding impact of high heart rate on our results is likely minimal because of the significant results ($P < 0.01$) with large intergroup differences.

STUDY LIMITATIONS. Given the absence of Holter monitoring, the rate of AF recurrence is likely to be underestimated. However, with systematic evaluation of heart rhythm at 6 and 12 months, we gained prospective data on the progression of cardiac rhythm. The irregular rhythm in AF creates artefacts and difficulty in image acquisition. However, with 286 examinations, our 3D serial evaluation allowed accurate evaluation of volume and function of the cavities. The high-volume rate mode used to acquire 3D data sets in this study, although feasible in atrial fibrillation, is not truly "guidelines compatible" and should be compared with other modes of 3D acquisition or other modalities of imaging to ensure the reproducibility of the measurements. Concerning changes in atrioventricular regurgitation, severity of valvular regurgitation was analyzed using the vena contracta method. In our practice, this variable was the most feasible for longitudinal evaluation. Indeed, at baseline or during follow-up, use of the effective regurgitant orifice area method was not possible for mild regurgitation (proximal isovelocity surface area radius or maximal jet velocity by continuous Doppler velocity were not feasible). Whether the changes in the sizes of the cavities and in cardiac function at 12 months were secondary to changes in cardiac rhythm or to a true physiological process of cavity remodeling is difficult to determine. Finally, 1 year is probably too short to document cardiac remodeling; 2-year follow-up is currently ongoing.

CONCLUSIONS

In our study, active restoration of SR was linked to anatomic (all atrial Vi, ES RV Vi) and/or functional (4 chambers) reverse remodeling of the cardiac chambers. Moreover, restoration of SR appears correlated with regression of functional atrioventricular regurgitation. Thus, in clinical practice, restoration of SR should be vigorously attempted to improve cavity reverse remodeling and severity of functional regurgitation in AF. Further investigations are necessary to determine the mechanisms and determinants of changes in valvular severity in AF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Restoration of sinus rhythm by cardioversion or ablation reduces LA and RA volumes and mitral and tricuspid regurgitation and improves atrial and ventricular function in patients with AF.

TRANSLATIONAL OUTLOOK: Further investigations are warranted to clarify the mechanisms of atrial, ventricular, and valvular dysfunction in patients with AF.

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APPENDIX For supplemental tables, please see the online version of this paper.