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Restoring Sinus Rhythm Reverses Cardiac Remodeling and Reduces Valvular

Regurgitation in Patients with Atrial Fibrillation

Brief Title: Reverse cardiac remodeling and functional regurgitation in 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 To explore the 3D 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 117 consecutive patients hospitalized for AF were examined using serial 3D transthoracic echocardiography at admission, 6 and 12 months (337 exams).

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, ED and 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. We found an improvement versus 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 was exclusively correlated to 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. (FASTRHAC: NCT 02741349)

CONDENSED ABSTRACT

The left atrial cavity is the most extensively studied cardiac chamber in atrial fibrillation (AF). We sought to explore, using 3D echocardiography, the 4 cardiac chamber cavities in AF according to change in cardiac rhythm at 12 months. Active restoration of sinus rhythm (SR) is linked to cardiac anatomical (all atrial volumes, end-systolic right ventricle volumes) and/or functional (4 chambers) reverse remodeling in the cardiac chambers and a reduction in severity of functional tricuspid and mitral regurgitation. Thus, management of AF should focus on restoration of SR to prevent both atrial and ventricular dysfunction and reduce functional atrioventricular regurgitation.

KEYWORDS three-dimensional echocardiography; atrial fibrillation; cardiac remodeling; functional regurgitation; cardioversion; ablation

ABBREVIATIONS

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

INTRODUCTION

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).

In AF, most of the literature on heart remodeling has focused on the left atrium (6), with only limited data on the left ventricle, right atrium, and right ventricle. The aims of this analysis, using data from the Thromboembolic and Bleeding Risk Stratification in Patients with Non-valvular Atrial Fibrillation (FASTRHAC) 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. NCT 02741349). The FASTRHAC methods have been previously published (7).

All consecutive patients (≥ 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 and 3D transthoracic echocardiography and transesophageal echocardiography data were collected over 2 years. CHA₂DS₂-VASc score (Congestive heart failure, Hypertension, Age ≥ 75 [doubled], Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism [doubled], Vascular disease, Age 65 to 74, Sex category [female]) 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- and 12-month follow-up. For the spontaneous SR, the cardiac rhythm was SR at each echocardiography evaluation during follow-up.

Right atrial and/or left atrial reverse remodeling was defined as a $\geq 15\%$ 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, Andover, MA, USA). Examinations were performed at admission and at 6 months and 12 months. The data were transferred and analyzed offline using a TOMTEC workstation (Image Arena; TOMTEC, Unterschleissheim, Germany) (L.S.D., I.B.T. and E.C.).

Two-dimensional and 3D measurements were analyzed following US 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 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 dataset. 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 right atrium, right ventricle, left atrium, and left ventricle (4D LV/LA analysis and 4D RV function software).

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

$$\text{3D right atrial emptying fraction} = (3\text{D ES RAV} - 3\text{D ED RAV}) / (3\text{D ES RAV})$$

$$\text{3D right ventricular ejection fraction} = (3\text{D ED RVV} - 3\text{D ES RVV}) / (3\text{D ED RVV})$$

$$\text{3D left atrial emptying fraction} = (3\text{D ES LAV} - 3\text{D ED LAV}) / (3\text{D ES LAV})$$

$$\text{3D left ventricular ejection fraction} = (3\text{D ED LVV} - 3\text{D ES LVV}) / (3\text{D ED LVV})$$

STATISTICAL ANALYSIS.

Continuous variables were compared using the non-parametric Kruskal-Wallis rank test at baseline and at both follow-ups. Categorical variables were compared using the chi-square or Fisher's 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 V12 (StataCorp, College Station, TX). $p < 0.05$ was considered statistically significant. The p values and 95% confidence intervals presented in this report have not been adjusted for multiplicity, and 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 characteristics of the population according to cardiac rhythm at 12 months are shown in **Table 1**. Seventy-two (61.5%) patients were male and the median 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 CHA₂DS₂-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 significant differences regarding troponin and D-dimer concentrations.

The spontaneous SR group had lower values for 3D atrial indexed volume (ED/ES RAVi and LAVi) and higher 3D ED RVVi values, with better 3D function of the cavities (right atrial emptying fraction, right ventricular ejection fraction, left atrial emptying fraction, and left ventricular ejection fraction). With the exception of 3D left atrial 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 2-dimensional 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 versus the AF group ($p<0.05$). There were no statistically significant differences between groups with regards to tricuspid regurgitation and aortic regurgitation vena contracta (**Supplemental Table 1**).

CHANGE IN ECHOCARDIOGRAPHIC VARIABLES DURING 1-YEAR FOLLOW-UP.

117 patients underwent echocardiography at admission, 103 patients at 6 months, and 117 patients at 12 months (a total of 337 exams). Offline analysis in 3D echocardiography was feasible in 286 (84.9%) exams. 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 left atrial 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 2-dimensional echocardiographic variables between baseline and follow-up.

Overall, 2-dimensional cavity volumes and function showed the same trends as those obtained with 3D echocardiography (**Supplemental Table 3**). The lowest severity of tricuspid and mitral regurgitation as assessed with vena contracta were 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 two-dimensional variables between months 6 and 12 (Supplemental Table 2 and 3).

In the AF group, there was a significant increase between month 6 and month 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 EmF. 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 month 6 and month 12 in the spontaneous SR group.

PREDICTORS OF RIGHT ATRIAL AND/OR LEFT ATRIAL REMODELING DURING 1-YEAR FOLLOW-UP.

The characteristics of the population according to right atrial and/or left atrial 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 left atrial emptying fraction, 3D right ventricular ejection fraction, and 3D left ventricular ejection fraction at admission were associated with right atrial and/or left atrial 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 left atrial 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 right atrial and/or left atrial reverse remodeling.

CLINICAL IMPLICATIONS OF CARDIAC CAVITY REMODELING.

Multimodality imaging using echocardiography, magnetic resonance imaging, and computed tomography is the cornerstone for evaluating AF. To date, the left atrial cavity is the most studied cardiac chamber in AF. In a healthy population, anatomical and functional evaluation of the left atrium 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 left atrium 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 right atrial (16,21) and right ventricular (32) variables appear correlated with risk of incident AF, whereas a few scattered studies have reported left ventricular, right ventricular (27), and right atrial (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 left ventricular 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 left atrial 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 right atrial and/or left atrial 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 left ventricular 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 diuretics 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. Whereas this could suggest an initial atrial stunning, the persistence of both atrial dysfunction at 12 months appears more likely correlated with an underlying atrial disease (i.e. 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 progression of cardiac rhythm. The irregular rhythm in AF creates artefacts and difficulty in image acquisition.. However, with 286 exams, our 3D serial evaluation allowed accurate evaluation of volume and function of the cavities. The high-volume rate mode used to acquire 3D datasets in this study, while 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.

Perspectives

Competency in Medical Knowledge: Restoration of sinus rhythm by cardioversion or ablation reduces left and right atrial volumes and mitral and tricuspid regurgitation and improves atrial and ventricular function in patients with atrial fibrillation (AF).

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

References

1. Hindricks G, Potpara T, Dagres N et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;42:373-498.
2. Donal E, Lip GY, Galderisi M et al. EACVI/EHRA Expert Consensus Document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. *Eur Heart J Cardiovasc Imaging* 2016;17:355-83.
3. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. *J Am Coll Cardiol* 2014;63:2335-45.
4. Shen MJ, Arora R, Jalife J. Atrial Myopathy. *JACC Basic Transl Sci* 2019;4:640-654.
5. Chen YC, Voskoboinik A, Gerche A, Marwick TH, McMullen JR. Prevention of Pathological Atrial Remodeling and Atrial Fibrillation: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2021;77:2846-2864.
6. Thomas L, Abhayaratna WP. Left Atrial Reverse Remodeling: Mechanisms, Evaluation, and Clinical Significance. *JACC Cardiovasc Imaging* 2017;10:65-77.
7. Soulat-Dufour L, Lang S, Ederhy S et al. Batrial remodelling in atrial fibrillation: A three-dimensional and strain echocardiography insight. *Arch Cardiovasc Dis* 2019;112:585-593.
8. Vahanian A, Beyersdorf F, Praz F et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2021;10.1093/eurheartj/ehab395.

9. Otto CM, Nishimura RA, Bonow RO et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021 Feb 2;77(4):450-500.
10. Zoghbi WA, Adams D, Bonow RO et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;30:303-371.
11. Tops LF, Delgado V, Bertini M et al. Left atrial strain predicts reverse remodeling after catheter ablation for atrial fibrillation. *J Am Coll Cardiol* 2011;57:324-31.
12. Lang RM, Badano LP, Mor-Avi V et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1-39 e14.
13. Lang RM, Badano LP, Tsang W et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. *J Am Soc Echocardiogr* 2012;25:3-46.
14. Habibi M, Samiei S, Ambale Venkatesh B et al. Cardiac Magnetic Resonance-Measured Left Atrial Volume and Function and Incident Atrial Fibrillation: Results From MESA (Multi-Ethnic Study of Atherosclerosis). *Circ Cardiovasc Imaging* 2016;9.
15. Hirose T, Kawasaki M, Tanaka R et al. Left atrial function assessed by speckle tracking echocardiography as a predictor of new-onset non-valvular atrial fibrillation: results from a prospective study in 580 adults. *Eur Heart J Cardiovasc Imaging* 2012;13:243-50.

16. Hubert A, Galand V, Donal E et al. Atrial function is altered in lone paroxysmal atrial fibrillation in male endurance veteran athletes. *Eur Heart J Cardiovasc Imaging* 2018;19:145-153.
17. Kosmala W, Saito M, Kaye G et al. Incremental value of left atrial structural and functional characteristics for prediction of atrial fibrillation in patients receiving cardiac pacing. *Circ Cardiovasc Imaging* 2015;8.
18. Lim DJ, Ambale-Ventakesh B, Ostovaneh MR et al. Change in left atrial function predicts incident atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J Cardiovasc Imaging* 2019;20:979-987.
19. Pathan F, Sivaraj E, Negishi K et al. Use of Atrial Strain to Predict Atrial Fibrillation After Cerebral Ischemia. *JACC Cardiovasc Imaging* 2018;11:1557-1565.
20. Schaaf M, Andre P, Altman M et al. Left atrial remodelling assessed by 2D and 3D echocardiography identifies paroxysmal atrial fibrillation. *Eur Heart J Cardiovasc Imaging* 2017;18:46-53.
21. Xie E, Yu R, Ambale-Venkaatesh B et al. Association of right atrial structure with incident atrial fibrillation: a longitudinal cohort cardiovascular magnetic resonance study from the Multi-Ethnic Study of Atherosclerosis (MESA). *J Cardiovasc Magn Reson* 2020;22:36.
22. Hof IE, Velthuis BK, Chaldoupi SM et al. Pulmonary vein antrum isolation leads to a significant decrease of left atrial size. *Europace* 2011;13:371-5.
23. Jeevanantham V, Ntim W, Navaneethan SD et al. Meta-analysis of the effect of radiofrequency catheter ablation on left atrial size, volumes and function in patients with atrial fibrillation. *Am J Cardiol* 2010;105:1317-26.

24. Montserrat S, Sitges M, Calvo N et al. Effect of repeated radiofrequency catheter ablation on left atrial function for the treatment of atrial fibrillation. *Am J Cardiol* 2011;108:1741-6.
25. Wylie JV, Jr., Peters DC, Essebag V, Manning WJ, Josephson ME, Hauser TH. Left atrial function and scar after catheter ablation of atrial fibrillation. *Heart Rhythm* 2008;5:656-62.
26. Muller H, Noble S, Keller PF et al. Biatrial anatomical reverse remodelling after radiofrequency catheter ablation for atrial fibrillation: evidence from real-time three-dimensional echocardiography. *Europace* 2008;10:1073-8.
27. Therkelsen SK, Groenning BA, Svendsen JH, Jensen GB. Atrial and ventricular volume and function evaluated by magnetic resonance imaging in patients with persistent atrial fibrillation before and after cardioversion. *Am J Cardiol* 2006;97:1213-9.
28. Azemi T, Rabdiya VM, Ayirala SR, McCullough LD, Silverman DI. Left atrial strain is reduced in patients with atrial fibrillation, stroke or TIA, and low risk CHADS(2) scores. *J Am Soc Echocardiogr* 2012;25:1327-32.
29. Leung M, van Rosendael PJ, Abou R et al. Left atrial function to identify patients with atrial fibrillation at high risk of stroke: new insights from a large registry. *Eur Heart J* 2018;39:1416-1425.
30. Obokata M, Negishi K, Kurosawa K et al. Left atrial strain provides incremental value for embolism risk stratification over CHA(2)DS(2)-VASc score and indicates prognostic impact in patients with atrial fibrillation. *J Am Soc Echocardiogr* 2014;27:709-716 e4.
31. Shih JY, Tsai WC, Huang YY et al. Association of decreased left atrial strain and strain rate with stroke in chronic atrial fibrillation. *J Am Soc Echocardiogr* 2011;24:513-9.

32. Chatterjee NA, Shah RV, Murthy VL et al. Right Ventricular Structure and Function Are Associated With Incident Atrial Fibrillation: MESA-RV Study (Multi-Ethnic Study of Atherosclerosis-Right Ventricle). *Circ Arrhythm Electrophysiol* 2017;10.
33. Marrouche NF, Kheirkhahan M, Brachmann J. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med* 2018;379:492.
34. Benfari G, Antoine C, Miller WL et al. Excess Mortality Associated With Functional Tricuspid Regurgitation Complicating Heart Failure With Reduced Ejection Fraction. *Circulation* 2019;140:196-206.
35. Mesi O, Gad MM, Crane AD et al. Severe Atrial Functional Mitral Regurgitation: Clinical and Echocardiographic Characteristics, Management and Outcomes. *JACC Cardiovasc Imaging* 2021;14:797-808.
36. Mutlak D, Khalil J, Lessick J, Kehat I, Agmon Y, Aronson D. Risk Factors for the Development of Functional Tricuspid Regurgitation and Their Population-Attributable Fractions. *JACC Cardiovasc Imaging* 2020;13:1643-1651.
37. Pluymaekers N, Dudink E, Luermans J et al. Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation. *N Engl J Med* 2019;380:1499-1508.
38. Danias PG, Caulfield TA, Weigner MJ, Silverman DI, Manning WJ. Likelihood of spontaneous conversion of atrial fibrillation to sinus rhythm. *J Am Coll Cardiol* 1998;31:588-92.
39. Geleris P, Stavratsi A, Afthonidis D, Kirpizidis H, Boudoulas H. Spontaneous conversion to sinus rhythm of recent (within 24 hours) atrial fibrillation. *J Cardiol* 2001;37:103-7.
40. Lindberg S, Hansen S, Nielsen T. Spontaneous conversion of first onset atrial fibrillation. *Intern Med J* 2012;42:1195-9.

41. Badano LP, Miglioranza MH, Mihaila S et al. Left Atrial Volumes and Function by Three-Dimensional Echocardiography: Reference Values, Accuracy, Reproducibility, and Comparison With Two-Dimensional Echocardiographic Measurements. *Circ Cardiovasc Imaging* 2016;9.
42. Soulat-Dufour L, Addetia K, Miyoshi T et al. Normal Values of Right Atrial Size and Function According to Age, Sex, and Ethnicity: Results of the World Alliance Societies of Echocardiography Study. *J Am Soc Echocardiogr* 2021;34:286-300.
43. Goette A, Kalman JM, Aguinaga L et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace* 2016;18:1455-1490.

Figure Legends

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

FIGURE 2 Change in 3D Volumes and 3D Function.

Differences in 3D indexed volumes (A, B, C) and 3D emptying fraction/ejection fraction (D, E, 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 versus 6M or admission versus 12M) with Wilcoxon matched-pairs signed-ranks test.

The errors bars are standard error 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; M = months; RA = right atrium; RV = right ventricle; SR = sinus rhythm.

FIGURE 3 Change in Vena Contracta.

Differences in tricuspid regurgitation and mitral regurgitation vena contracta 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 vena contracta during follow-up.

* $p < 0.05$, comparison of 2D vena contracta with baseline (admission versus 6M or admission versus 12M) with Wilcoxon matched-pairs signed-ranks test.

The errors bars are standard error of mean.

No corrections for multiple testing were applied.

TR = tricuspid regurgitation; M = months; MR = mitral regurgitation.

CENTRAL ILLUSTRATION Reverse Cardiac Remodeling/ Improvement of Regurgitation After Restoration of SR

At 1 year of FU in AF, active restoration of SR induced cardiac anatomical (atrial Vi, ES RV Vi) and/or functional (4 chambers) reverse remodeling and a regression of functional TR and MR.

An active management of AF focused on restoration of SR, could prevent both atrial and ventricular cardiomyopathy and reduce functional atrioventricular regurgitation.

RA = right atrium; RV = right ventricle; LA = left atrium; LV = left ventricle; TR = tricuspid regurgitation; MR = mitral regurgitation; SR = sinus rhythm.

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, yrs	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)‡	19 (61.3)§	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	10 (25.6)	14 (28.8)	5 (16.1)	0.39
Medical history				
Myocardial infarction	12 (64.1)	15 (31.9)‡	3 (9.7)¶	0.021
Heart failure	13 (33.3)	4 (8.5)‡	1 (3.2)¶	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	0.031
Renal insufficiency	7 (18.0)	1 (2.1)	0¶	0.003
Cancer	6 (15.4)	5 (10.6)	5 (18.1)	0.73

	AF (n=39)	Active SR (n=47)	Spontaneous SR (n=31)	p Value
Obstructive sleep apnea syndrome	5 (12.8)	2 (4.3)	1 (3.2)	0.27
CHA ₂ DS 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) ‡	27 (87) ¶	<0.0001
AF classification				
Paroxysmal	10 (26)	17 (36.2)	31 (100.0) §¶	<0.0001
Persistent	29 (74.0)	30 (63.8)	0	
Reason for hospitalization				<0.0001
Isolated AF	22 (56.4)	25 (53.2)	28 (90.3) §¶	
AF + heart failure	14 (35.9)	21 (44.7)	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 ‡	21 (67.7) §	<0.0001
Intervention (cardioversion and/or ablation)	21 (53.9)	47 (100)	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) §¶	0.0059

	AF (n=39)	Active SR (n=47)	Spontaneous SR (n=31)	p Value
Hemoglobin A1C, % (n=37/44/30)	6.0 (5.7, 6.3)	5.8 (5.5, 6.3)	5.5 (5.1, 5.7)§¶	0.0008
Glomerular filtration rate, ml/min/1.73 m ² (MDRD)	67 (49, 79)	71 (66, 83)	82 (65, 99)¶	0.0090
B-type natriuretic peptide, pg/ml (39/47/30)	298 (190, 424)	252 (103, 506)	90 (45, 186)§¶	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	-
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)§¶	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)¶	0.013
3D RA EmF, % (n=34/41/29)	24.4 (21.1, 25.4)	25.4 (20.2, 25.4)	42.5 (33.9, 42.5)	0.0001

	AF (n=39)	Active SR (n=47)	Spontaneous SR (n=31)	p Value
	29.3)	36.4)	46.4)§¶	
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)§¶	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)§¶	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)§¶	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)¶	0.0094
3D LA EmF, % (n=35/41/29)	29.3 (25.8, 32.1)	24.7 (19.6, 30.9)‡	42.6 (36.8, 46.8)§¶	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)¶	0.17
3D LVEF, % (n=35/41/29)	41.7 (36.7, 47.8)	38.0 (30.0, 46.0)	55.2 (52.2, 58.2)§¶	0.0001

	AF (n=39)	Active SR (n=47)	Spontaneous SR (n=31)	p Value
	50.8)	47.5)	56.9) §¶	

‡p<0.05 between AF group and active SR group.

§p<0.05 between active SR group and spontaneous SR group.

¶p<0.05 between AF group and spontaneous SR group.

||Defined as more than two glasses of wine per day or equivalent.

No corrections for multiple testing were applied.

AF = atrial fibrillation; 3D = three-dimensional; ES = ventricular end-systole; ED = ventricular end-diastole; EmF = emptying fraction; LVEF = left ventricular ejection fraction; MDRD = Modification of Diet in Renal Disease; SR = sinus rhythm.

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

Parameters	Univariate analysis		Multivariable analysis	
	Odds ratio (95% CI)	p Value	Odds ratio (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

3D = 3-dimensional; AF = atrial fibrillation; CI = confidence interval; ED = end-diastolic; EmF = emptying fraction; LAEmF = left atrial emptying fraction; LAVi = left atrium volume indexed to body surface area; LVEF = left ventricular ejection fraction; RAEmF = right atrial emptying fraction; RAVi = right atrium volume indexed to body surface area; RVEF = right ventricular ejection fraction.

Admission

117 patients hospitalized for paroxysmal or persistent AF

Non-spontaneous restoration of SR (n=86)

Spontaneous restoration of SR <24 h after admission (n=31)

Integrated AF management (cardioversion and/or ablation and/or pharmacological treatment)

Integrated AF management (ablation and/or pharmacological treatment)

12 months

Absence of restoration of SR at 12 months

Active restoration of SR at 12 months

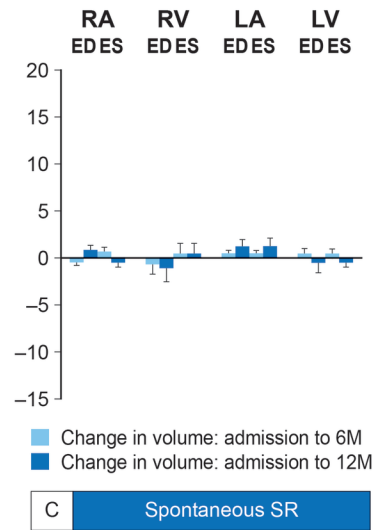
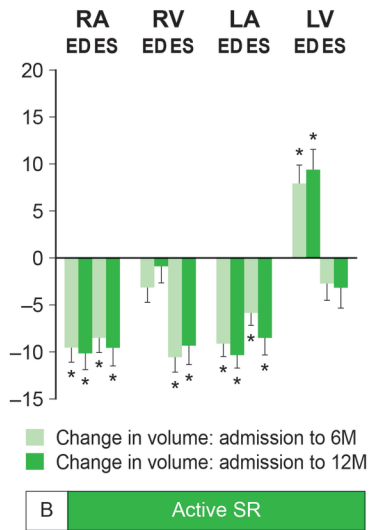
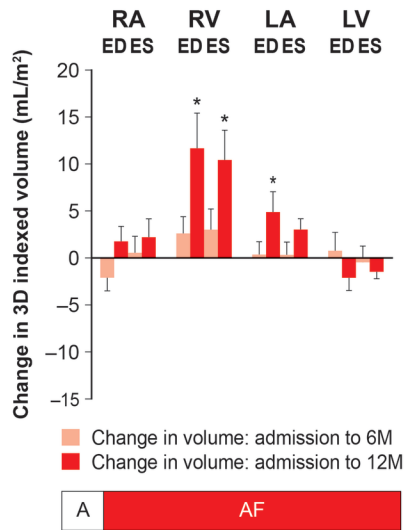
Maintenance of SR at 12 months

AF group
(n=39)

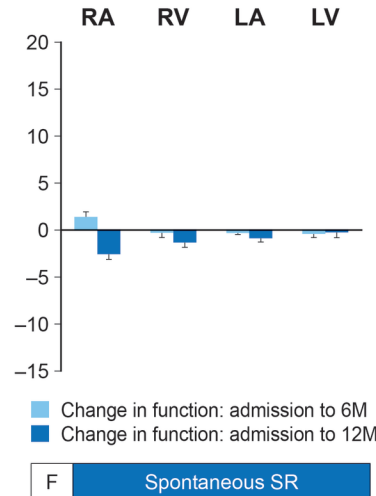
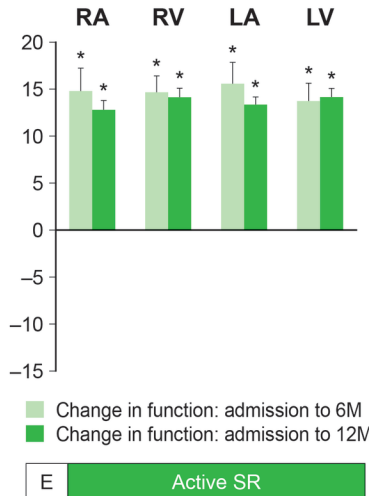
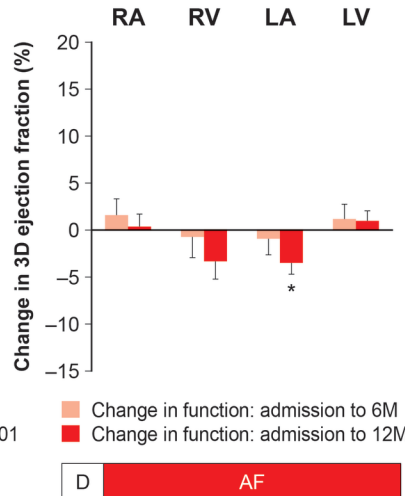
Active SR group
(n=47)

Spontaneous SR group
(n=31)

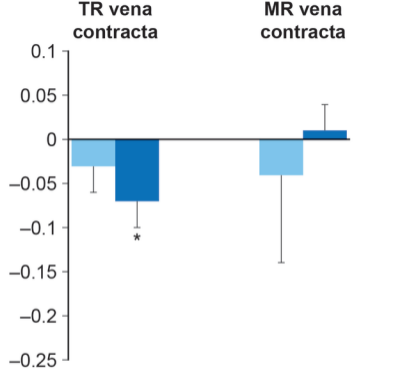
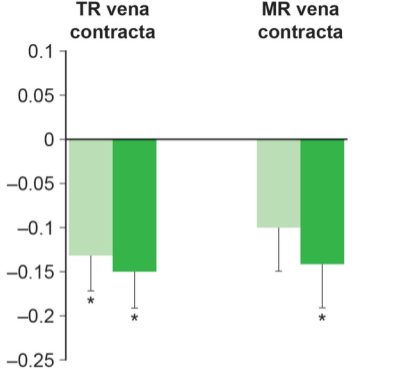
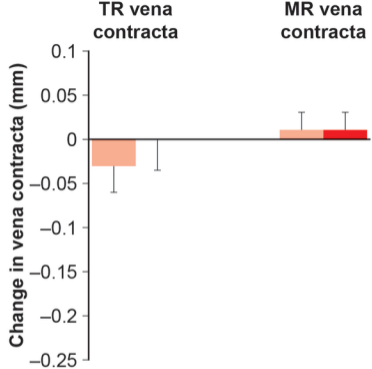
Change in 3D volumes



Change in 3D function



*p<0.01



Change in vena contracta: admission to 6M
 Change in vena contracta: admission to 12M
 *p<0.05

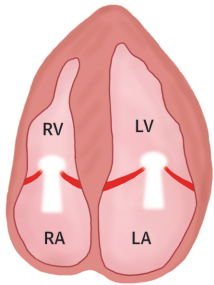
Change in vena contracta: admission to 6M
 Change in vena contracta: admission to 12M

Change in vena contracta: admission to 6M
 Change in vena contracta: admission to 12M

A AF

B Active SR

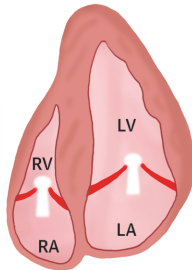
C Spontaneous SR



Atrial Fibrillation



**Active restoration
of sinus rhythm**



**Anatomical and
functional reverse
remodeling**

**Regression of
functional
TR and MR**



**Prevention of
atrial and
ventricular
cardiomyopathy**