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ABSTRACT

Background: Functional mitral regurgitation (FMR) and atrial fibrillation (AF) are frequent heart failure (HF) complications. Cardiac resynchronization therapy (CRT) can improve FMR; however, little is known about the influence of AF on FMR improvement.

Objective: To investigate the mechanisms and impact of baseline AF on FMR improvement after CRT.

Methods: CRT recipients with HF, AF or sinus rhythm (SR) at baseline with moderate or severe FMR, were included from an ongoing registry. LA, mitral annular (MA) and left ventricular (LV) dimensions were evaluated echocardiographically. FMR improvement was defined as ≥1 grade decrease from baseline to 6 months follow-up. Clinical and echocardiographic measurements were performed at baseline and 6 months follow-up.

Results: 419 patients (66±8 years, 73% male) were analyzed. At 6 months follow-up, FMR improved in 145 (45.6%) patients with SR, vs. 31 (30.7%) in AF patients (p=0.011). Despite similar LV reverse remodeling at 6 months after CRT (LV end-systolic volume decreased by 32.1±43.2 ml in the SR group, and by 27.7± 6.3 ml in those with AF; p=0.353), patients with SR exhibited smaller LA volumes (63.0±26.5 ml vs. 103.1±41.0 ml; p<0.001) and MA diameters (42.3±5.6 mm vs. 46.1±5.8 mm; p<0.001), compared to AF patients.

Conclusion: FMR improvement is more common in CRT recipients in SR, vs. AF, despite a similar degree of LV remodeling. LA volume and MA diameter are greater in the AF group, causing the negative impact of AF on FMR improvement in CRT, as well as indicating a potential therapeutic target, i.e. AF rhythm control.

Key words: functional mitral regurgitation, atrial fibrillation, remodeling, heart failure, cardiac resynchronization therapy

INTRODUCTION

Functional mitral regurgitation (FMR) is a frequent complication of heart failure, with a prevalence of 50-65%.[1, 2] Global or regional left ventricular (LV) dysfunction or remodeling can cause FMR by tethering of the mitral valve leaflets and impaired closing forces.[3] Atrial fibrillation (AF) is another common manifestation of heart failure (increasing in prevalence from 5% in New York Heart Association (NYHA) class I to 50% in class IV), and it may contribute to the severity of FMR through left atrial (LA) and mitral annular dilatation.[4-6] Both AF and FMR worsen the prognosis of patients with heart failure, although the impact of AF is more controversial.[2, 7, 8]

Heart failure patients with AF who remain symptomatic despite optimal medical therapy (NYHA functional class III and ambulatory IV), with wide QRS complex (≥130 ms) and reduced LV ejection fraction (LVEF≤35%), are candidates for cardiac resynchronization therapy (CRT).[4, 9] CRT not only improves LV systolic function, but can also decrease FMR by a variety of mechanisms.[3, 9] In addition, CRT has been associated with a reduction of LA dimensions and a decrease in the burden of AF.[10] Since AF may influence the severity of FMR in heart failure patients through LA enlargement and mitral annular dilatation, the purpose of the present study was to investigate if the presence of baseline AF has an impact on the extent of FMR improvement which occurs after CRT.

METHODS

Study population and design

Heart failure patients with moderate to severe FMR at baseline who subsequently received CRT, were selected from an ongoing clinical registry.[11] Patients with heart failure, who remain symptomatic despite receiving maximum tolerated doses of optimal medical therapy, are included in the registry on implantation of a CRT device. The institutional review board

approved the study and waived the need for written informed consent for retrospective analysis of clinically acquired data anonymously handled. All data used for the present study were acquired for clinical purposes and handled anonymously. Demographic, clinical, electrocardiographic and echocardiographic data are collected. Patients were divided according to the baseline rhythm: AF vs. sinus rhythm (SR). AF at baseline was classified according to current guidelines: i) paroxysmal ii) persistent iii) long-standing persistent and iv) permanent.[12] Clinical, electrocardiographic and echocardiographic assessment was performed at baseline (before CRT implantation), and repeated at 6 months follow-up. Ischemic heart failure was defined by the presence of coronary artery disease. The following functional parameters were evaluated: NYHA functional class, quality of life (Minnesota Living with Heart Failure Questionnaire) and (when patients' functional status permits) 6-minute walk test. Patients were excluded if they underwent mitral valve repair, replacement or percutaneous mitral valve repair at any time, or if the cause of mitral regurgitation was organic.

CRT implantation technique

The right atrial and ventricular leads were placed via a standard subclavian or cephalic vein approach. Coronary sinus venography was used to guide the LV lead implantation. All leads were subsequently connected to a dual-chamber, biventricular CRT-device. CRT devices with defibrillator function were implanted in the majority of patients (96%), while 4% received a CRT device without a defibrillator function. Patients were followed-up at regular intervals in the heart failure clinic, with concurrent interrogation of device function. Atrioventricular delays were empirically set at 120-140 ms, while interventricular delays were similarly set at 0 ms. CRT device optimization was performed at the discretion of the treating physician during follow-up visits.

Echocardiographic acquisition and data analysis

Transthoracic echocardiograms were performed in the left lateral decubitus position with a commercially available echocardiographic system (E9 or VIVID 7, General Electric Vingmed Ultrasound, Milwaukee, USA). ECG-triggered M-mode, 2-dimensional and Doppler data were collected and digitally stored in order to facilitate off-line analysis (EchoPac 113, General Electric Vingmed Ultrasound, Milwaukee, USA). LV end-systolic (LVESV) and end-diastolic (LVEDV) volumes were measured on 2-dimensional apical 2- and 4-chamber views according to the Simpson's method, where after LVEF was calculated.[13] The LA volume was measured during mid-systole in optimised apical 2- and 4-chamber views, while the mitral valve annulus diameter was similarly measured during mid-systole in an apical 4-chamber view and a parasternal long-axis view (Figure 1). Both qualitative and quantitative parameters were employed to grade FMR severity according to contemporary recommendations on an ordinal scale, with none = 0, mild = 1, moderate = 2, moderate to severe = 3 and severe = 4.[14] Improvement in FMR was defined as ≥1 grade decrease from baseline to 6-month follow-up.

Statistical analysis

Continuous data are presented with means and standard deviations, while categorical data are expressed in numbers and percentages. Independent samples t-tests were used to compare continuous variables and χ^2 tests, as well as Fisher's exact tests (as appropriate) for comparison of categorical variables. A binary logistic regression analysis was performed to investigate the association of rhythm at baseline with improvement of FMR, correcting for LBBB, angiotensin-converting enzyme (ACE) inhibitor use, rhythm at baseline and biventricular pacing >90%. Analyses were performed with SPSS for Windows, version 23.0

(SPSS, Armonk, NY, USA). All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

RESULTS

Baseline patient characteristics

Of 1570 heart failure patients treated with CRT, 419 patients (mean age was 66±8 years, 73% male) presented with moderate to severe FMR. Baseline characteristics of patients in AF (n=101) and patients in SR (n=318) are presented in Table 1. Amongst patients with baseline AF, 52 (51%) had paroxysmal, 44 (44%) permanent, 4 (4%) persistent and 1 (1%) long-standing persistent AF. 33 (33%) of patients with baseline AF underwent direct current cardioversion before CRT implantation, 10 (10%) His bundle ablation and 1 (1%) AF catheter ablation.

Improvement in FMR severity after CRT

CRT induced comparable reductions in LVESV (from baseline to 6 months) for patients in SR at baseline and in patients in AF at baseline: a mean LVESV decrease of 32.1±43.2 ml (18.1%) vs. 27.7±36.3 ml (18.6%), was respectively observed; p=0.353 (Figure 2, Table 2). Despite similar extent of LV reverse remodelling, improvement in FMR (from baseline to 6 months) was more frequently observed among patients in SR at baseline as compared to patients in AF at baseline (145 (45.6%) vs. 31 (30.7%), respectively; p=0.011) (Figure 3). Interestingly, after 6 months of CRT, patients in SR at baseline demonstrated a smaller LA volume than those in AF at baseline (63.0±26.5 ml vs. 103.1±41.0 ml, respectively; p<0.001) (Table 2), as well as a greater decrease in LA size (10.2% vs. 2.3%, respectively, p=0.047) (Table 2). Similarly, patients with SR at baseline evidenced a smaller mitral annulus diameter (measured in the parasternal, long-axis view) (34.5±4.8 mm vs. 39.6±5.2 mm, respectively;

p<0.001) and a greater degree of mitral annulus remodeling (4.4% vs. 0.0%, respectively, p<0.001) at 6 months post-CRT, compared to those with AF at baseline (Table 2). On multivariable, logistic regression analysis, SR at baseline remains independently associated with FMR improvement after CRT (adjusted OR 1.69, 95% 1.02-2.83, p=0.04). These results suggest that the atriogenic component of FMR needs to be corrected on top of LV reverse remodeling to optimize the rate of FMR improvement after CRT implantation.

DISCUSSION

Heart failure patients with AF before CRT implantation, experienced less improvement in FMR as compared to CRT recipients in SR at baseline. This difference was observed despite a similar extent of LV reverse remodeling after 6 months. Importantly, LA volume and mitral annular dimension were significantly larger in the baseline AF group as compared to the baseline SR group at 6 months after CRT, suggesting an atrial component in the pathophysiology of FMR not fully reversed by CRT.

LV remodeling and FMR improvement in CRT: the impact of AF

LV reverse remodeling defined by a reduction in LVESV has been reported in 62-85% of heart failure patients treated with CRT and is associated with superior survival at follow-up.[15, 16] LV reverse remodeling is one of the mechanisms by which CRT improves FMR. However, CRT reduces the amount of FMR by other mechanisms, including resynchronization of atrioventricular, inter- and intraventricular contraction, an increase in mitral leaflet closing forces which leads to improved leaflet coaptation.[3, 17, 18]

In a study of 673 CRT recipients (162 with AF), no significant difference in the change in LVESV was found between SR and AF groups (p = 0.828).[19] Our data confirm that there is no appreciable difference in the amount of LV reverse remodeling between CRT recipients

with AF and SR at baseline, while a greater reduction in FMR is noted at 6 months in heart failure patients with SR at baseline who are treated with CRT, compared to AF at baseline. The negative impact of baseline AF on the extent of FMR reduction, can therefore not be ascribed only to a differential effect on LV remodeling, and another mechanism should be considered.

Influence of AF on FMR

It is proposed that AF worsens FMR by means of 1) mitral annular dilatation and 2) atriogenic leaflet tethering (Figure 4).[20, 21] Longstanding AF is firmly linked to LA enlargement.[22] Structurally, the mitral annulus is closely related to the LA, and due to the absence of a reinforcing fibrous skeleton, the posterolateral annulus is susceptible to stretching by longitudinal LA muscle fibers when the LA enlarges.[5] Mitral annular dilatation leads to a reduced coaptation area of the mitral leaflets, and subsequent worsening of FMR.[20] AF may worsen FMR by another mechanism, namely atriogenic leaflet tethering, which implies stretching of the posterior mitral leaflet across the LV wall by LA enlargement, with subsequent displacement/tethering of the anterior mitral valve leaflet away from the papillary muscles.[21] Two studies have reported an association between AF on the one hand, and an increased mitral annular area and FMR on the other hand.[23] In the present study we found evidence to support these mechanisms in the context of CRT, namely patients with baseline AF having an enlarged LA, less decrease in LA volume, a larger mitral annulus diameter, less mitral annular remodeling and worse FMR at 6 months follow-up, compared to patients in SR at baseline. The decrease in mitral annular diameter is much more pronounced when measured in the parasternal long axis view, compared to the apical four chamber view. This likely reflects the fact that long axis measurement transects the fixed annulus and the

unsupported part, while the apical four chamber measurement may still a second, fixed part of the mitral fibrous skeleton (Supplemental material).

Effects of CRT on LA and mitral annular size

LA reverse remodeling has been documented after CRT, especially in responders to CRT.[10, 24] The LA volume decreased from 66.8±25.2 cm^3 to 58.4±27.8 cm^3 in CRT responders (defined as a reduction of ≥10% LVESV) (p=0.014) in a study of 107 CRT recipients.[24] The effect of CRT on the mitral annulus per se, has not been extensively investigated. In a study of 30 patients with heart failure and FMR, CRT led to an improvement of the mitral annulus area deformation (defined as diastolic mitral annulus area minus systolic mitral annulus area divided by diastolic mitral annulus area, percent) in responders (defined as a patients having a reduction of ≥ 15% LVESV) from 19±10% to 25±8%, while there was no change in non-responders (from 22±9% to 22±9%).[18] Conversely, in another study including 26 patients with FMR undergoing CRT, there was no immediate change in the mitral annulus diameter.[25]

As far as the authors are aware, there are no reports in the literature which describe the differential effect of AF versus SR at baseline on LA and mitral annulus reverse remodeling after CRT. Our data demonstrate that LA volume and mitral annular dimension are significantly larger after CRT in patients with moderate to severe FMR and AF at baseline, compared to those in SR at baseline.

In summary, baseline AF therefore appears to exert an inhibitory effect on LA and mitral annular reverse remodeling after CRT in patients with FMR. This resulted in less improvement in FMR in CRT recipients with baseline AF as compared to patients in SR at baseline.

Clinical implications

Since FMR response to CRT is of prognostic importance, and this response is impaired by AF, mitigating the negative influence of AF on FMR is an attractive therapeutic strategy. In 330 patients with permanent AF who received CRT, 34 (10.3%) spontaneously recovered SR by 4 months.[26] In contrast, in a study of 74 patients (27% with persistent AF and 73% with permanent AF), CRT did not induce spontaneous conversion to SR in any patient at 6 months of follow-up.[27] With the current findings, it is unclear if awaiting a spontaneous return to SR after CRT is the optimal strategy. Various additional treatment options could be considered to restore SR in AF patients, including pharmacological and electrical cardioversion, as well as catheter ablation. In a study by Gertz et al. 53 patients with moderate to severe FMR who underwent AF catheter ablation, the mitral annular dimension was significantly larger in those with recurrent AF compared to patients who remained in SR (3.48±0.34 cm vs. 3.24±0.32 cm, respectively; p=0.06) at one year.[28] In that same study, the LA volume was larger in patients with recurrent AF as compared to patients who remained in SR (66.4±18.4 cm3 vs. 52.4±12.7 cm^3, respectively; p=0.02) at one year follow-up.[28] Moreover, significant FMR at one year follow-up was observed in 24% of patients in SR as compared to 82%, in patients with AF at one year follow-up (p=0.005).[28] Although this study was not performed in patients undergoing CRT, the results suggest that AF ablation has the potential to reduce FMR in CRT recipients by reducing LA volume and mitral annular diameter.

Currently, one trial investigated AF recurrence after radiofrequency catheter ablation in patients who previously underwent CRT; Di Biase et al. randomized CRT recipients to AF ablation or amiodarone use, with a minimum follow-up of 2 years.[6] The recurrence of AF was significantly lower in the patients undergoing ablation as compared to the patients using amiodarone (30% vs. 66%, respectively; p<0.001) and a significant mortality difference was observed in favour of ablation (8% vs. 18%; p=0.037).[6] The concept of an atrial myopathy

has gained attention in recent years, with those having more advanced electromechanical atrial disease (e.g. fibrosis, visualised with cardiac magnetic resonance imaging) responding less well to catheter ablation.[29] It is not inconceivable that patients with advanced atrial myopathy and/or long-standing AF will also respond suboptimally to ablative therapy in terms of FMR reduction. Even though the success rate of AF ablation is more variable in persistent and long-standing AF, mitral annular reverse remodeling and a decrease in AF recurrence in CRT patients were seen in those studies where such patients were included.[6, 28] Recently, the Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial demonstrated lower all-cause mortality and heart failure hospitalization in heart failure patients with AF who underwent catheter ablation, when compared to medical therapy.[30] Of the patients who underwent ablation, 27% had a CRT device in situ.[30] Although reduction in FMR was not reported, this trial provides further support for the role of catheter ablation in the management of AF in heart failure patients, including those with CRT.

Study limitations

This was a single-center, retrospective study. The severity of FMR can be influenced by different hemodynamic conditions, although only hemodynamically stable patients were included in the current analysis. The variability of LV volumes and ejection fraction and LA volumes with 2-dimensional echocardiography is well known. Slight changes in the acquisition of the LV and LA data at follow-up may lead to a relative wide standard deviation of the change in volume.

CONCLUSIONS

Improvement of FMR is more often observed in CRT recipients in SR at baseline, as compared to patients with AF at baseline, despite a similar degree of LV reverse remodeling at 6 months after CRT. LA volume and mitral annular diameter are larger at 6 months in the patients with AF at baseline, suggesting that these mechanisms may relate to the adverse effect of AF on FMR improvement following CRT. AF rhythm control (especially by means of catheter ablation) is therefore a potential therapeutic target to improve FMR after CRT in patients with AF, although the response in those with permanent AF may be variable, compared to paroxysmal AF.

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Table 1. Patient baseline characteristics according rhythm (atrial fibrillation or sinus rhythm)

	AF (n=101)	SR (n=318)	p-value
Age (years)	70±8	66±10	<0.001
Male, n (%)	85 (84.2)	222 (70.0)	0.004
Ischemic etiology, n (%)	53 (52.5)	185 (58.2)	0.357
LBBB, n (%)	41 (40.6)	225 (70.8)	<0.001
QRS duration at baseline (ms)	157.0±34.0	156.0±29.3	0.768
NYHA class, n (%)			
- **I**	3 (3.0)	8 (2.5)	0.731
- **II**	24 (23.8)	83 (26.1)	0.696
- **III**	63 (62.4)	201 (63.2)	0.906
- **IV**	11 (10.9)	26 (8.2)	0.422
6 MWT (m)	309.4±106.4	317.9±116.9	0.549
QoL score	33.2±19.1	33.4±19.2	0.949

Diabetes mellitus, n (%)	18 (17.8)	63 (19.8)	0.773
eGFR <60 ml/min/1.73 m^2, n (%)	47 (46.5)	142 (44.7)	0.819
LVEF (%)	26.2±8.4	25.0±7.6	0.173
LVEDV (ml)	198.7±72.4	233.0±83.9	<0.001
LVEDVi (ml/m^2)	101.2±36.0	120.5±41.2	<0.001
LVESV (ml)	149.0±62.9	177.3±74.4	0.001
LVESVi (ml/m^2)	76.0±31.5	91.8±37.7	<0.001
LA volume (ml)	105.5±37.7	70.3±25.8	<0.001
Mitral anular diameter (mm)	47.7±5.4	44.0±5.3	<0.001
Medication, n (%)			
- **Diuretic**	90 (89.1)	263 (82.7)	0.158
- **Digoxin**	29 (28.7)	47 (14.8)	0.003
- **β-blocker**	62 (61.4)	236 (74.2)	0.017
- **Mineralocorticoid antagonist**	50 (49.5)	152 (47.8)	0.819
- **ACE-inhibitor/ARB**	81 (80.2)	287 (90.3)	0.013

Continuous variables are mean ± standard deviation. AF, atrial fibrillation, ACE, angiotensin-converting enzyme, ARB, angiotensin receptor blocker, eGFR, estimated glomerular filtration rate, LA, left atrial, LBBB, left bundle branch block, LVEF, left ventricular ejection fraction, LVEDV, left ventricular end-diastolic volume, LVEDVi, indexed left ventricular end-diastolic volume, LVESV, left ventricular end-systolic volume, LVESVi, left ventricular end-systolic volume, 6 MWT, six-minute walk test, NYHA, New York Heart Association class, QoL, quality of life score, SR, sinus rhythm

Table 2. Changes in LVESV, LA volume and mitral anular diameters, according to baseline rhythm

	AF	SR	p-value
LVESV (ml)			
- **Baseline**	149.0±62.9	177.3±74.4	0.001
- **Six months**	121.4±52.2	145.2±65.4	0.001
- **Change**	27.7±36.3	32.1±43.2	0.353
- **% change**	18.6	18.1	0.725
LA volume (ml)			
- **Baseline**	105.5±37.7	70.3±25.8	<0.001
- **Six months**	103.1±41.0	63.0±26.5	<0.001
- **Change**	2.4±29.4	7.2±22.7	0.133
- **% change**	2.3	10.2	0.047
Mitral anular diameter (A4C view) (mm)			
- **Baseline**	47.7±5.4	44.0±5.3	<0.001
- **Six months**	46.1±5.8	42.3±5.6	<0.001

- **Change**	1.6±4.8	1.7±5.2	0.820
- **% change**	3.4	3.9	0.731
Mitral anular diameter (PSLAX view) (mm)			
- **Baseline**	39.6±5.2	36.1±4.7	<0.001
- **Six months**	39.6±5.2	34.5±4.8	<0.001
- **Change**	0.0±4.2	1.6±3.7	0.001
- **% change**	0.0	4.4	<0.001

A4C: apical four-chamber, AF: atrial fibrillation, LA: left atrial, LVESV: left ventricular end-systolic volume, PSLAX: parasternal long-axis, SR: sinus rhythm

Figure 1: measurement of mitral annulus diameter

Mitral valve annulus diameter, measured in mid-systole in an apical 4-chamber view (red, dumbbell marker) and left atrial volume, measured in mid-systole in an apical 4-chamber view (blue grid) (A). Mitral annulus diameter, measured in mid-systole in a parasternal, long-axis view (red, dumbbell marker) (B).

Figure 2: changes in left ventricular end-systolic volume (LVESV)

Change in LVESV from baseline to six months after cardiac resynchronization therapy in patients with sinus rhythm versus atrial fibrillation at baseline. Vertical bars represent standard error of the mean.

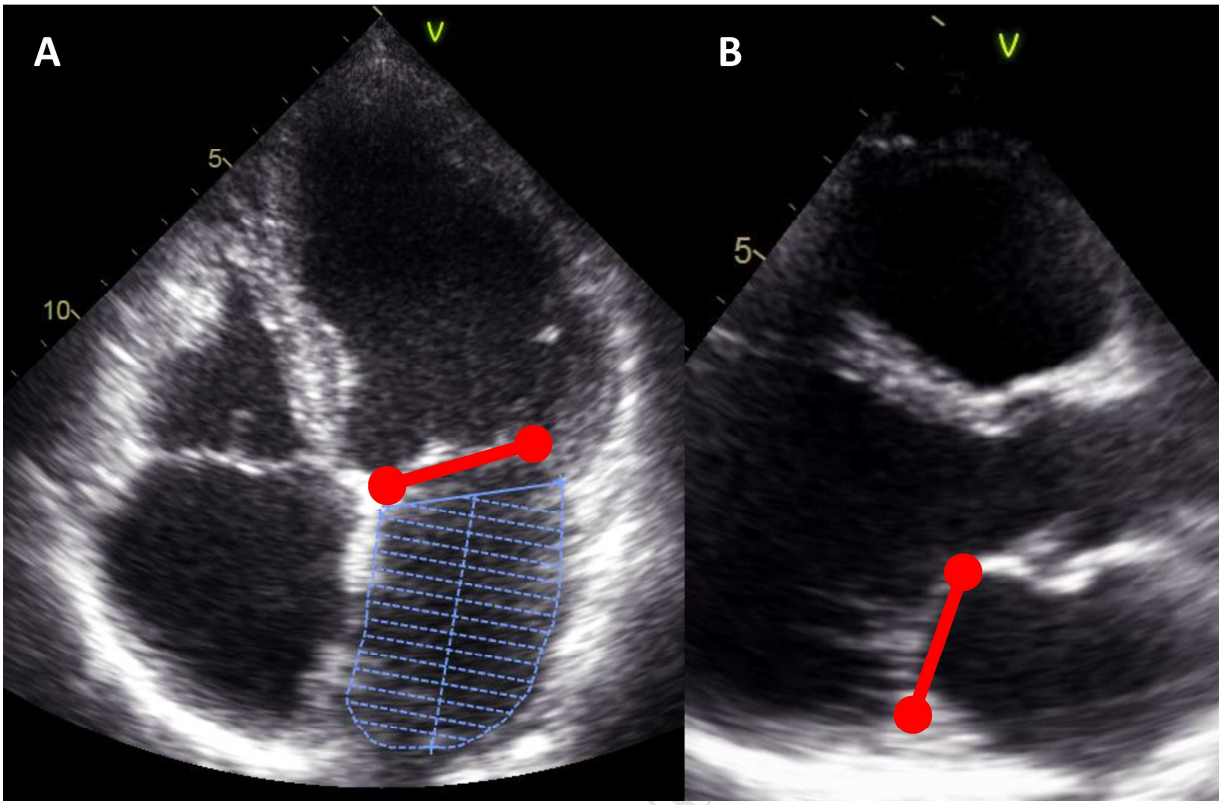
Figure 3: improvement in functional mitral regurgitation

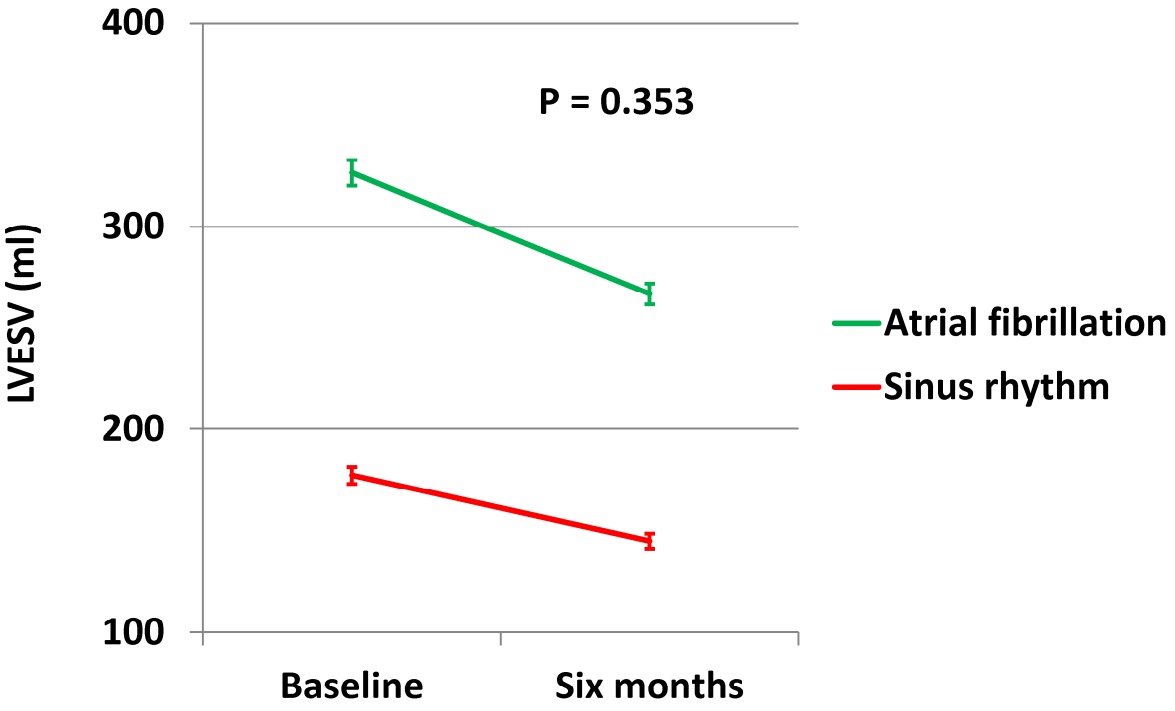
Percentage (%) of patients demonstrating improvement of functional mitral regurgitation after cardiac resynchronization therapy, according to baseline rhythm. SR, sinus rhythm; AF, atrial fibrillation. Improvement in FMR (from baseline to 6 months) was more frequently observed among patients in SR at baseline (45.6%), compared to patients in AF at baseline (30.7%).

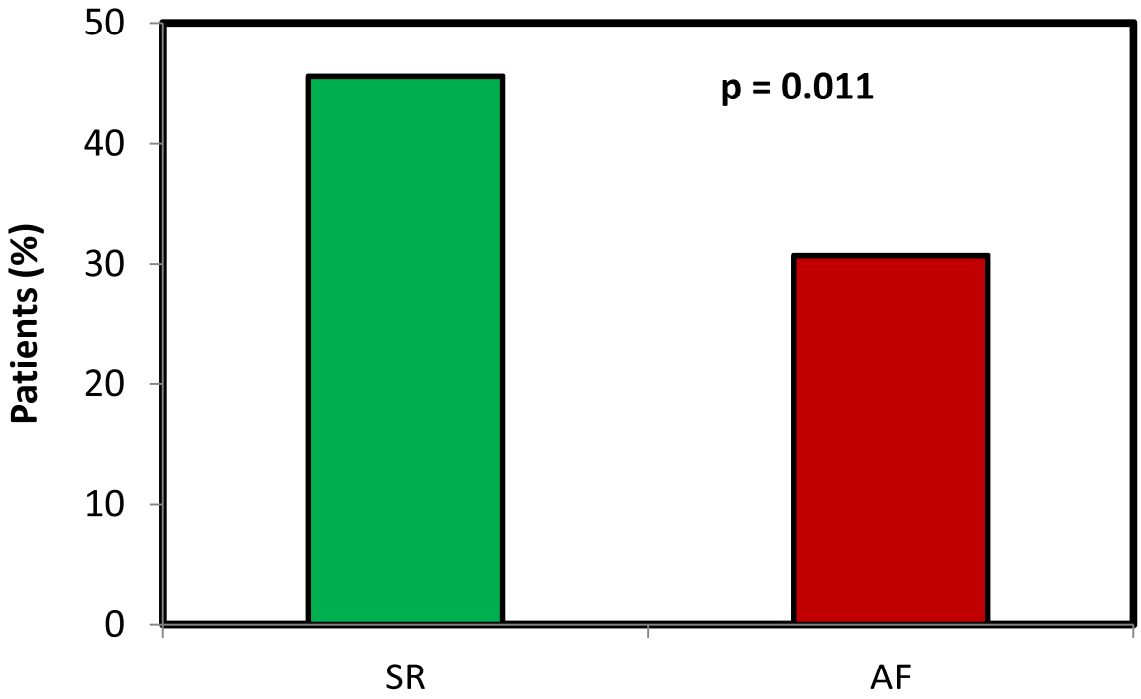
Figure 4: mechanism of AF impact on FMR in CRT recipients

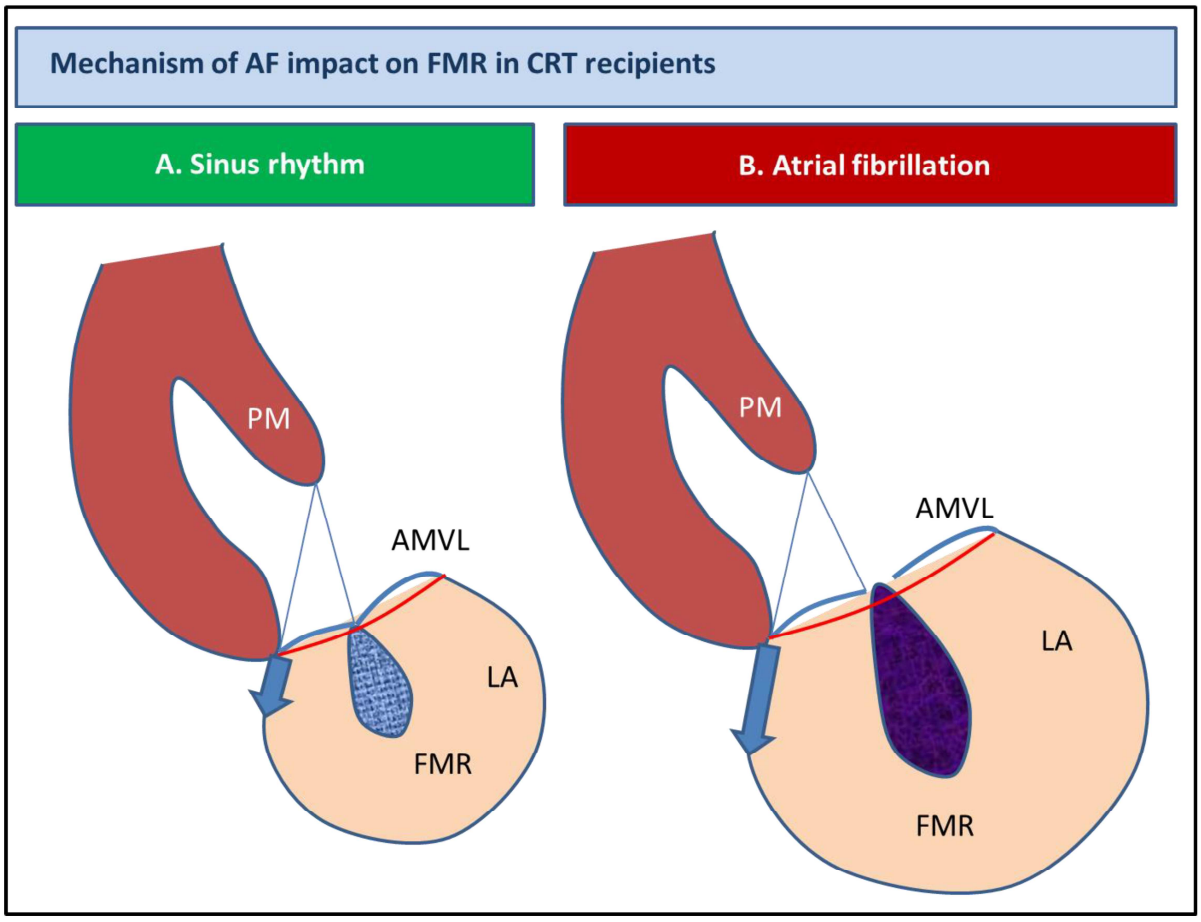
The mitral annulus (indicated in red) is closely related to the LA, and due to the absence of a reinforcing fibrous skeleton, the posterolateral annulus is susceptible to stretching by longitudinal LA muscle fibers when the LA enlarges (blue arrows indicate stretching forces of the LA on the posterolateral annulus). Mitral annular dilatation leads to a reduced coaptation area of the mitral leaflets (gap between the leaflets in B), and subsequent

worsening of FMR. A CRT recipient with SR at baseline is shown in A), and a patient with AF at baseline in B). AF: atrial fibrillation; AMVL: anterior mitral valve leaflet; CRT: cardiac resynchronization therapy; FMR: functional mitral regurgitation; LA: left atrium; PM: papillary muscle; SR: sinus rhythm








Mechanism of AF impact on FMR in CRT recipients
A. Sinus rhythm
B. Atrial fibrillation
PM
AMVL
LA
FMR
PM
AMVL
LA
FMR