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Changes in left atrial size and function early after cardiac resynchronization therapy as assessed by conventional two-dimensional echocardiography

Silvia Lupu[1], Adriana Mitre[2,3], Ioana Sus[1,2], Roxana Rudzik[2], Ildiko Beke[2], Dan Dobreanu[1,2]

[1]Department of Physiology, University of Medicine and Pharmacy, [2]Emergency Institute of Cardiovascular Disease and Transplant, [3]Centre for Advanced Medical and Pharmaceutical Research, [4]5th Department of Internal Medicine, University of Medicine and Pharmacy, Târgu Mureş, Romania

Abstract

Aims: Cardiac resynchronization therapy (CRT) was shown to improve left atrial (LA) size and function within months after the procedure. We aimed to assess the impact of CRT on left atrial (LA) size and function within days after the procedure. **Materials and methods:** Twenty-eight consecutive patients with CRT were evaluated before the procedure and within 3 days afterwards, and 25 of them were also examined at three months. Echocardiography was performed to assess LA size and function: LA volumes indexed to body surface (LAVIs) were measured at different moments during the cardiac cycle: ventricular end-systole – maximum LAVI (LAVImax), before atrial systole (LAVIpreA), and at ventricular end-diastole – minimum LAVI (LAVImin). These measurements were further used to calculate LA function parameters: LA total emptying fraction, active emptying fraction and passive emptying fraction. **Results:** LAVImax decreased within days after the procedure – 45.5 mL/m^2 (38.2-56.7) vs. 42.9 mL/m^2 (32.1- 56.2), $p < 0.05$, as did LAVImin – 27.1 mL/m^2 (22.9-41.9) vs. 25.9 mL/m^2 (17.8-38.1), $p < 0.05$, and LAVIpreA – 40.0 mL/m^2 (31.3-53.0) vs. 35.5 mL/m^2 (25.8-49.1), without significant changes in functional parameters. All LAVIs were correlated to the diastolic filling time/RR interval ratio after CRT, but not before. **Conclusions:** LAVIs may be reduced within days after the implant procedure in responders to CRT, while atrial functional parameters remain unchanged. Correlations beween LAVIs and the diastolic filling time/RR interval ratio after CRT suggest that early optimization of atrio-ventricular and ventriculo-ventricular delays may have a positive and immediate impact on LA size.

Keywords: left atrial indexed volumes; left atrial function; cardiac resynchronization therapy; heart failure; echocardiography

Introduction

During the last decade, left atrium indexed volumes (LAVIs) and LA function parameters assessment by echocardiography gained interest as markers of diastolic dysfunction and increased left ventricular (LV) filling pressures [1-2], and as predictors of outcome in patients with heart failure [3-6].

Current techniques for assessing LA size include two- or three-dimensional measurements of LAVI at different moments during the cardiac cycle, which can also be used for quantifying the reservoir, conduit, and pump function of the LA. Atrial strain assessment by either tissue Doppler or speckle tracking has also been proposed for quantifying LA function.

Lately, there has been a growing interest for assessing LA size and function in patients with heart failure who undergo cardiac resynchronization therapy (CRT). Increased maximum LA indexed volume (LAVImax) emerged as a reliable predictor of heart failure and death, or all-cause mortality, in the The Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchroni-

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Corresponding author: Silvia Lupu, MD, PhD
Department of Physiology, University of Medicine and Pharmacy of Târgu Mureş
38, Gheorghe Marinescu St, 540139,
Târgu Mureş, Romania
Phone:+40744913163
E-mail: sil_lupu@yahoo.com;
silvia.lupu@umftgm.ro

zation Therapy (MADIT-CRT) trial [5] and in smaller studies focused on patients with CRT [6]. In addition, in a recently published research, LA reverse-remodeling, defined as a reduction of ≥10% in LAVImax at six months follow-up, was a reliable predictor of cardiovascular outcomes [7]. Moreover, in this study, patients who exhibited LA reverse-remodeling without LV reverse-remodeling had similar outcomes to those who had both LA and LV reverse-remodeling [7], which seems to suggest that LA size assessment is as valuable if not even more valuable than the study of LV size.

Several studies evaluated the correlation between LA function and clinical improvement at three and six months after CRT. LA size and function were quantified by conventional B-mode methods and the assessment of LA strain by tissue Doppler [8] and speckle tracking, respectively [9]. CRT responders exhibited LA size reduction and LA functional improvement.

Although data has begun to pool regarding the changes in LA size and function in CRT patients, to our knowledge, there is currently no published research on the early impact of CRT on the LA. In the current study, we aimed to explore the immediate changes, within 3 days after the implant procedure, on LA size and function, assessed by conventional, widely available, two-dimensional echocardiography parameters in patients with heart failure and CRT.

Material and methods

Patients

We examined 28 consecutive patients who were hospitalized in our institution between February 2014 and February 2016. Of the 28 patients, 25 were enrolled in the study, as three of the patients did not attend all the programmed visits, due to non-medical issues.

Patients were enrolled provided they had symptomatic heart failure ≥NYHA II despite optimal tolerated medical therapy, left ventricular ejection fraction (LVEF) of ≤35%, left bundle branch block (LBBB) with QRS width of at least 120 msec or right bundle branch block with a QRS duration of at least 150 msec, with indication for CRT according to the 2013 European Society of Cardiology guidelines [10]. Patients who had permanent or persistent atrial fibrillation at any visit, before or after CRT, those who had primary mitral valve disease, as well as patients with a life expectancy of less than a year due to either heart failure or other terminal disease, or poor echocardiographic window were excluded. Patients who refused to take part in the research were not enrolled.

All patients were submitted to a thorough investigation protocol including history, physical examination, complete blood count and standard serum biochemistry, 12-lead ECG, chest X-ray, the 6-minute walk test, the Minnesota Living with Heart Failure Questionnaire, echocardiography, and CRT-P/CRT-D device follow-up. The atrio-ventricular and ventriculo-ventricular delays were adjusted using a standard protocol in order to ensure a physiological depolarization pattern of the endocardium. Adjustments were guided by atrio-ventricular and ventriculo-ventricular intervals recorded using right atrial (RA), right ventricular (RV) and LV leads, standard 12-leads electrocardiograms and pulsed-wave Doppler assessment of the mitral flow on echocardiography, avoiding E and A wave fusion and truncated A waves. The iterative method was used to adjust atrio-ventricular delays, as previously described [11]. Echocardiographic measurements reported in this study were only performed after optimal ECG and transmitral flow patterns have been achieved, at the first examination after CRT. At three months, examinations were performed with the same atrio-ventricular and ventriculo-ventricular delays.

The same investigation protocol was applied three times: first – one day before CRT (baseline assessment), second – within 3 days after the procedure, third – at three months. The latter visit was required for assessing response to CRT, which was defined as NYHA class improvement and a reduction in LV end-systolic volume ≥15% by comparison with pre-CRT values [12-14]. At the baseline assessment, all enrolled patients were on optimal medical therapy, in maximum tolerated doses, which remained unchanged until the second evaluation, performed within 3 days after the procedure.

All patients signed an informed consent form. The study was conducted according to the principles of the Declaration of Helsinki and approved by the Research Ethics Committee of the University.

Echocardiography methods

Echocardiographic examinations were performed using a Vivid S5, BT 10, GE Medical Systems echocardiograph with a 2.5 MHz transducer. The ECG trace was simultaneously recorded using lead II for dyssynchrony parameters assessment and a Lewis lead to help guide LA volumes measurement.

Left atrial volumes and function assessment

LA size was quantified based on the LA diameter measured from the parasternal long axis view. The maximum LAVI (LAVImax) was measured at ventricular end-systole. LAVI before atrial systole LAVIpreA was measured before the P wave on the ECG and minimum LAVI (LAVImin) was measured at the end of ventricular diastole, immediately after mitral valve closure, as previously described [15]. Based on these volumes, functional parameters were derived to assess the reservoir, conduit

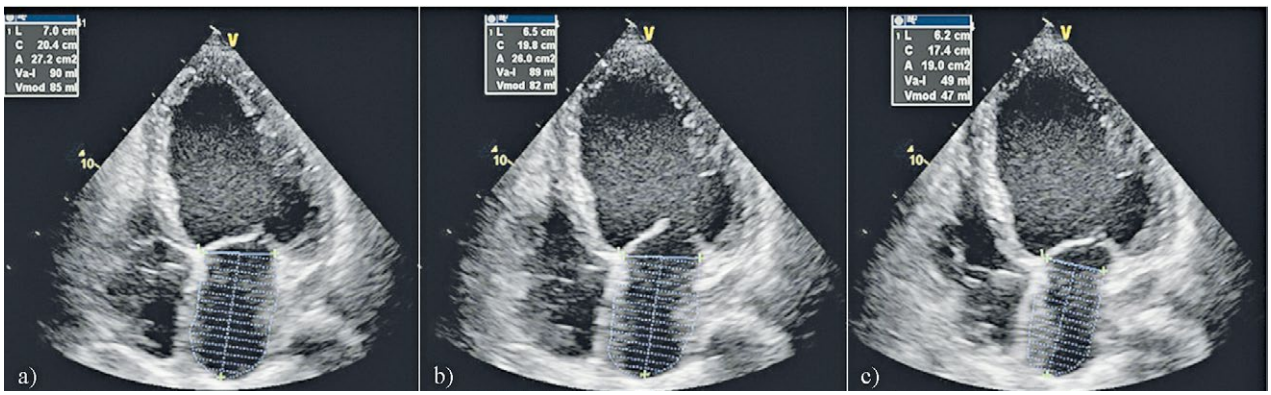

Fig 1. Measurements of left atrial volumes by two dimensional echocardiography: a) maximum left atrial volume, at ventricular end-systole: b) preA left atrial volume, measured before the P wave on the ECG; c) minimum left atrial volume, at ventricular end-diastole, immediately after mitral valve closure.

and pump function of the LA. For the reservoir function the total emptying fraction was calculated as (LAVImax–LAVImin)/LAVImax × 100. For the conduit function the passive emptying fraction was calculated as (LAVImax – LAVIpreA)/LAVImax × 100. For the pump function, the active emptying fraction was calculated as (LAVIpreA–LAVImin/LAVIpreA) × 100 [15]. LAVI measurements are represented in figure 1.

Left ventricular systolic and diastolic function assessment

Left ventricular volumes were measured from the apical 4-chamber view and indexed to body surface. LVEF was determined based on Simpson's modified rule. Diastolic function was assessed by transmitral flow parameters – maximum velocities of E and A waves, E/A ratio and E wave deceleration time (EDT). The transmitral flow was recorded from the apical 4-chamber view by placing a 2 mm sample volume at the tip of the mitral leaflets, at a sweep speed of 100 cm/sec on three distinct cardiac cycles, during postexpiratory apnoea. Diastolic dysfunction severity was graded as mild for E/A ≤0.8 and E wave velocity ≤50 cm/s, moderate (pseudonormal pattern) for E/A ≤0.8 and E >50 cm/s or 0.8< E/A <2, or severe (restrictive pattern) if E/A ≥2. Filling pressures were assessed by the E/E' ratio and were considered normal for an E/E' ratio <8, and elevated for an E/E' ratio >8 [16]. To calculate E/E' we used the average of E' values measured on the interventricular septum and lateral wall.

Mechanical dyssynchrony assessment

We assessed mechanical dyssynchrony by the following parameters: 1) for atrio-ventricular dyssynchrony – the diastolic filling time/RR interval ratio; the diastolic filling time was measured from the beginning to the end of the transmitral flow, recorded by pulsed wave Doppler from the apical 4-chamber view; atrio-ventricular dyssynchrony was considered present for a duration of diastole/duration of cardiac cycle ratio <40% [14,17]; 2) for inter-ventricular asynchrony – the inter-ventricular motion delay (IVMD), calculated as the difference between the aortic (APT) and pulmonary pre-ejection times (PPT); the pre-ejection times were measured from the beginning of the QRS complex to the beginning of the LV and right ventricular outflows, respectively, recorded by pulsed wave Doppler; interventricular dyssynchrony was considered present at an IVMD >40 msec [14,20]; 3) for intra-ventricular asynchrony – the septal to posterior wall motion delay (SPWMD), recorded by color tissue Doppler and M-mode, combined; values of >130 msec were considered indicative of intraventricular dyssynchrony; the delay between the maximum posterior wall contraction (time from QRS onset to maximum posterior wall contraction, recorded by color tissue Doppler and M-mode from the parasternal long axis view) and the beginning of diastole (time from QRS onset to transmitral flow onset, recorded by pulsed wave Doppler); positive differences were considered an indicator of intraventricular dyssynchrony; presence of apical rocking and septal flash, as previously described [14,18].

All recordings for time measurements were performed at a sweep speed of 100 cm/sec.

Additional echocardiographic parameters

Mitral regurgitation was classified as mild, moderate or severe according to the recommendations of the European Association of Cardiovascular Imaging [19]. The probability of pulmonary hypertension and the estimated systolic pulmonary artery pressure were assessed by measuring maximal tricuspid regurgitation velocity and inferior vena cava diameter and inspiratory collapse, as previously recommended. The probability of pulmonary hypertension was considered low for a maximum tricuspid regurgitation velocity ≤2.8 m/sec, in the absence of other echocardiographic signs of pulmonary hyperten-

sion; intermmediate for maximum tricuspid regurgitation velocities ≤2.8 m/sec, with other signs of pulmonary hypertension, or without such signs and maximum velocities between 2.9-3.4 m/sec, and high, if maximum tricuspid regurgitation velocities were >3.4 m/sec, or between 2.9-3.4 m/sec if additional signs of pulmonary hypertension were present [20].

Statistical analysis

Data were tested for normality using the Shapiro-Wilk test. Variables with normal distribution were reported as mean value ± standard deviation (SD), while data with non-gaussian distribution were reported as median and interquartile range. Considering the low number of patients and the fact that most variables had non-gaussian distribution, non-parametric tests were further used. Comparisons were made using Wilcoxon's and McNemar's tests, according to the type of data (continuous or dichotomial), while correlations were assessed by the Spearman's test. Linear regression analysis was also performed. Results were considered statistically significant for $p < 0.05$. All statistical analysis was performed using the MedCalc software, version 14.8 (MedCalc Software bvba, Ostend, Belgium).

Results

Twenty-eight patients were enrolled, but three were excluded, as they did not attend the three months visit, due to non-medical issues. The final study group consisted of 25 patients.

At the baseline evaluation, 24 out of the 25 patients (96%) had LBBB, 23 of which had a QRS duration ≥130 msec. A single patient had right bundle branch block with a QRS width of 180 msec. Most patients had echocardiographic evidence of ventricular dyssynchrony; the median value of IVMD was 66 (48.8-75.8) msec, and most patients had apical rocking (n=23, 92%) and/or septal flash (n=21, 84%). Median SPWMD values were 270 (185-315) msec. Few patients had ischaemic dilated cardiomyopathy (DCM) (n=2, 8%) and/or increased probability of pulmonary hypertension, as assessed by echocardiography (n=3, 12%). All baseline data are recorded in Table I.

Based on the final evaluation at three months after the implant procedure, all patients were considered responders to CRT, according to the previously described criteria. The LV end-systolic volume indexed diminished from 174 (136.5-199.0) ml/m^2 before the procedure to 122 (103.0-161.0) ml/m^2 at the three months visit, p=0.0001. There was also a significant improvement in NYHA class (p=0.0001).

The comparative analysis of clinical and paraclinical data collected before and within 3 days after the procedure revealed statistically significant improvements, regarding the NYHA class and 6-minute walk test distances, which increased from 410 m (363.5-477.5) before CRT to 500 m (430.0-527.5) after the procedure. The comparative analysis of echocardiography-derived data yielded significant changes early after CRT. There was a reduction in end-systolic and end-diastolic left ventricular diameters and volumes, and improved LVEF – 22.0 (19.5-25.0) *vs* 28.0 (26.0-30.5), p=0.0001. Moreover, mitral regurgitation severity regressed after CRT.

Among LA size parameters, all recorded LAVIs were significantly reduced, as was maximum LA area – 20.5 (16.4-24.3) cm^2 vs. 18.8 (15.3-23.4) cm^2, $p<0.05$, despite the fact that changes in minimum and preA LA areas did not reach statistical significance. LA function parameters did not improve within days after the procedure (Table II).

Table I. Demographical, clinical and electrocardiographic characteristics at the baseline visit

Parameter	CRT patients N= 25
Demographical and clinical data	
Age (SD), years	60±12
Gender, female, n%	5 (20%)
Weight (SD), kg	80±15
Body surface area (SD), m^2	1.90±0.1
Functional NYHA class ≥ III, n (%)	14 (56%)
CRT-D, n (%)	9 (36%)
Ischemic DCM, n (%)	2 (8%)
High probability of pulmonary hypertension, n (%)	3 (12%)
ECG parameters	
QRS duration (IQR), msec	160 (160 – 180)
LBBB, n (%)	24 (96%)
RBBB, n (%)	1 (4%)

SD, standard deviation; NYHA, New York Heart Association; CRT-D, Cardiac Resynchronization Therapy Defibrillator; DCM, dilated cardiomyopathy; IQR, interquartile range; LBBB, left bundle branch block; RBBB, right bundle branch block; IVMD, interventricular motion delay

Table II. Comparative analysis of clinical and echocardiographic data before and within days (early) after CRT

Parameter	Pre-CRT (n=25)	Days after CRT (n= 25)	p
Weight, kg	80±15	79±15	NS
Body surface area, m^2	1.9±0.1	1.9±0.1	NS
Functional NYHA class (I/II/III/IV), n	0/11/11/3	1/20/4/0	**0.0001**
QRS duration, msec	160 (160-180)	140 (137-160)	**0.0001**
6MWTD, m	410 (363.5-477.5)	500 (430.0-527.5)	**<0.001**
Echocardiography			
LVEDD, mm	70 (65-76)	69 (65-74,3)	**<0.01**
LVESD, mm	63.5 (56.5-68.5)	60.0 (53.5-65.5)	**<0.01**
LVEDV indexed, ml/m^2	111.5 (89.9-138.8)	106.4 (81.7-132.2)	**<0.01**
LVESV indexed, ml/m^2	83.9 (64.5-111.0)	78.1 (53.9-95.1)	**< 0.0001**
LVEF, %	22.0 (19.5-25.0)	28.0 (26.0-30.5)	**0.0001**
LA diameter, mm	47 (46.0-51.3)	46 (41.5-49.3)	**<0.001**
LAVImax, ml/m^2	45.5 (38.2-56.7)	42.9 (32.1-56.2)	**<0.05**
LAA max, cm^2	25.3 (22.1-29.8)	23.4 (20.4-28.9)	NS
LAVImin, ml/m^2	27.1 (22.9-41.9)	25.9 (17.8-38.1)	**<0.05**
LAAmin, cm^2	20.5 (16.4-24.3)	18.8 (15.3-23.4)	NS
LAVIpreA, ml/m^2	40.0 (31.3-53.0)	35.5 (25.8-49.1)	**<0.05**
LAApreA, cm^2	24.0 (20.1-26.9)	20.4 (18.0-26.5)	**<0.05**
Total emptying fraction, %	34.3 (28.0-41.2)	34.0 (28.2-44.2)	NS
Passive emptying fraction, %	15.5 (11.2-19.0)	15.4 (10.8-19.5)	NS
Active emptying fraction, %	22.5 (6.1-31)	25.7 (13.4-34.6)	NS
Mitral E/A	0.77 (0.6-1.33)	0.68 (0.55-1.17)	NS
Mitral E/E'	10.3 (8.9-14)	10.6 (8.9-12.6)	NS
EDT, msec	147 (117-235)	216 (161-244)	NS
Degree of diastolic dysfunction (mild/moderate/severe)	11/3/7*	14/4/3	NS
Mitral regurgitation severity (none/mild/moderate/severe)	3/5/13/4	5/10/10/0	**0.001**
RAVI, ml/m^2	25.9 (21.3-29.7)	25.4 (22.0-29.4)	NS
RAA, cm^2	17.0 (15.3-19.9)	17.2 (15.3-19.0)	NS
sPAP, mmHg	36.5 (18.0-53.0)	22.5 (17.0-38.0)	**<0.01**
APT, msec	163 (141.3-180.8)	148 (118-175.5)	**<0.05**
IVMD, msec	66 (48.8-75.8)	14 (5.3-29.3)	**< 0.0001**
SPWMD, msec	270 (185-315)	45 (40-95)	**< 0.0001**
(Q-PP) – (Q-Mi), msec	-90.5 (-147.5/-33.5)	-141.5 (-254.5/-104.5)	**<0.01**
Diastolic filling time/RR interval, %	42 (38.8-49.8)	50 (41.0-53.33)	**<0.05**
Apical rocking, n (%)	23 (92%)	10 (40%)	**<0.001**
Septal flash, n (%)	21 (84%)	9 (36%)	**<0.001**

NYHA, New York Heart Association; CRT-D, cardiac resynchronization therapy defibrillator; LBBB, left bundle branch block; 6MWTD, six minute walk test distance; LVEDD, left ventricle end-diastolic diameter; LVESD, left ventricle end-systolic diameter; LVEDV, left ventricle end-diastolic volume indexed; LVESV, left ventricle end-systolic volume indexed; LVEF, left ventricle ejection fraction; LA, left atrium; LAVI max, maximum left atrium volume indexed; LAA max, maximum left atrial area; LAVI min, minimum left atrium volume indexed; LAA min, minimum left atrial area; LAVI preA, left atrial volume indexed before atrial systole; LAA preA, left atrium area before atrial systole; EDT, E wave deceleration time; RAVI, right atrium volume indexed; RAA, right atrium area; sPAP, systolic pulmonary artery pressure; APT, aortic pre-ejection time; IVMD, interventricular motion delay; Q-PP, time from onset of QRS complex to maximum left ventricular posterior wall contraction; Q-Mi, time from QRS onset to mitral valve opening; SPWMD, septal to posterior wall motion delay. *In 4 patients, E and A wave were fused at the baseline evaluation; therefore they were excluded from the analysis of diastolic function parameters.

Correlations between echocardiographic LA size or function parameters, and LV function parameters were further tested, revealing a specific trend: before CRT, all LAVIs (minimum, maximum and preA) were significantly correlated with the severity of diastolic dysfunction, the EDT and the E/E' ratio, as well as the severity of mitral regurgitation; after CRT, the correlations of all three volumes to EDT and the severity of mitral regurgitation were lost, while a new one, between maximum and minimum LAVI and the diastolic filling time/RR interval ratio emerged. All significant correlations were moderate (Table III). None of the analyzed parameters correlated

Table III. Univariate analysis – correlations between morphological and functional parameters of the left atrium with clinical and echocardiographic parameters before and early after CRT

LAVImax	**Pre- CRT**		**Post-CRT**	
	Spearman's rho	**p**	**Spearman's rho**	**p**
Diastolic dysfunction degree	0.512	**<0.01**	0.459	**<0.05**
EDT	-0.575	**<0.01**	-0.353	NS
E/E' ratio	0.594	**<0.01**	0.518	**<0.05**
LVEF	-0.055	NS	-0.248	NS
Diastolic filling time/RR interval	0.218	NS	0.441	**<0.05**
Mitral regurgitation degree	0.479	**<0.01**	0.389	NS
6MWTD	0.188	NS	-0.274	NS
LAVIpreA				
Diastolic dysfunction degree	0.458	**<0.05**	0.408	**<0.05**
EDT	-0.547	**<0.01**	-0.240	NS
E/E' ratio	0.519	**<0.01**	0.462	**<0.05**
LVEF	-0.081	NS	-0.242	NS
Diastolic filling time/RR interval	0.175	NS	0.350	NS
Mitral regurgitation degree	0.420	**<0.05**	0.358	NS
6MWTD	0.070	NS	0.358	NS
LAVImin				
Diastolic dysfunction degree	0.594	**<0.01**	0.511	**<0.01**
EDT	-0.628	**0.001**	-0.379	NS
E/E' ratio	0.462	**<0.05**	0.460	**<0.05**
LVEF	-0.242	NS	0.074	NS
Diastolic filling time/RR interval	0.209	NS	0.417	**<0.05**
Mitral regurgitation degree	0.499	**<0.01**	-0.348	NS
6MWTD	-0.229	NS	0.102	NS
Total emptying fraction (Left atrial expansion index)				
Diastolic dysfunction degree	-0.596	**<0.01**	-0.582	**<0.01**
EDT	0.612	**<0.01**	0.366	NS
E/E' ratio	-0.229	NS	-0.209	NS
LVEF	0.074	NS	0.073	NS
Diastolic filling time/RR interval	-0.138	NS	-0.338	NS
Mitral regurgitation degree	-0.348	NS	-0.217	NS
6MWTD	0.102	NS	0.088	NS
Active emptying fraction				
Diastolic dysfunction degree	-0.813	**<0.0001**	-0.553	**<0.01**
EDT	0.473	**<0.05**	0.473	**<0.01**
E/E' ratio	-0.240	NS	-0.240	NS
LVEF	0.217	NS	0.203	NS
Diastolic filling time/RR interval	-0.126	NS	-0.284	NS
Mitral regurgitation degree	-0.508	**<0.01**	-0.258	NS
6MWTD	0.082	NS	0.163	NS
Passive emptying fraction				
Diastolic dysfunction degree	0.237	NS	**-0.127**	**NS**
EDT	-0.156	NS	**-0.042**	**NS**
E/E' ratio	0.067	NS	-0.201	NS
LVEF	-0.126	NS	0.053	NS
Diastolic filling time/RR interval	0.033	NS	-0.078	NS
Mitral regurgitation degree	0.280	NS	-0.192	NS
6MWTD	0.177	NS	0.043	NS

LAVImax, maximum left atrial volume indexed; LAVIpreA, left atrial volume indexed before atrial systole; LAVI min, minimum left atrial volume indexed; EDT, E wave deceleration time; LVEF, left ventricular ejection fraction; 6MWTD, 6 minute walk test distance; RR, RR interval on the electrocardiogram.

to the LVEF, 6-minute walk test distance, NYHA class or the quality of life score.

Linear regression analysis yielded significant correlations between LAVIs and the degree of diastolic dysfunction before and after CRT, independently of mitral regurgitation severity and the diastolic filling time/RR interval ratio. Moreover, LAVI max, min and preA correlated to the degree of diastolic dysfunction independently of mitral regurgitation severity before CRT ($p<0.0001$) and of the diastolic filling time/RR interval ratio after the procedure ($p<0.0001$).

Discussions

In the current study, LA volumes reduced significantly within days after CRT, without major changes in LA volumes-derived functional parameters. Clinical status, assessed by the NYHA functional class and 6-minute walk test distance, was also improved. Moreover, statistically significant improvements were recorded in LV size and systolic function parameters, mitral regurgitation severity, and dyssynchrony parameters, while diastolic dysfunction parameters, other than LAVIs, were not significantly changed.

All 25 patients were considered responders to CRT when reassessed at three months, which is not surprising considering the fact that, overall, patients in the study group had favorable characteristics for becoming responders. Most of the patients had LBBB QRS morphology at baseline, with fairly wide QRS (median value of 160 msec); as previously shown by other studies, including the EchoCRT trial, decreased QRS width is associated with poor outcomes after CRT [20-21]. Only a single patient in the study group had a QRS width of 120 msec, and favourable anatomy, allowing the insertion of the coronary sinus lead into a postero-lateral vein; this patient was also a responder to CRT according to previously described criteria.

Also, most enrolled patients had mechanical dyssynchrony on echocardiography. For instance, the median values of IVMD were quite high in the study group, and increased IVMD was previously shown to associate with response to CRT [22] and predict good outcomes [23]. In addition to that, previous studies have shown that the presence of apical rocking and septal flash before CRT was associated with better response to the procedure [24,25], and these features occurred in most patients of our study group. Moreover, few patients had poor predictors of response to CRT, such as ischemic DCM [23] and increased probability of pulmonary hypertension [26], as assessed by echocardiography.

The main purpose of the current study was, however, to assess the changes in LAVIs and LA function immediately after CRT and to explore the pathophysiological background of these changes. A couple of factors have previously been shown to contribute to reduce LAVI in CRT patients, such as LV diastolic function improvement [27], the regression of LV filling pressures or diminished mitral regurgitation [28]. However, neither the transmitral flow-derived diastolic function parameters, nor the E/E' ratio improved significantly within days after CRT, while the severity of mitral regurgitation was significantly reduced, but no longer correlated to LAVI after the implant procedure.

The lack of improvement in LV diastolic function parameters within days after CRT may be justified by the fact that, within such a short period of time, the intrinsic properties of the myocardium did not change significantly. Currently, data regarding the molecular mechanisms behind reverse remodeling are scarce; however, one study showed a significant increase in messenger RNA levels of α-myosin and in the ratio of α-/-β myosin heavy chains in responders to CRT, who also exhibited increased sarcoplasmic reticulum calcium ATP-ase 2α messager RNA levels and elevated SERCA/phospholamban ratio [29]. These mechanisms have been proposed for justifying myocardial reverse remodeling in responders to CRT and are unlikely to occur at such an early stage. Moreover, this phenomenon could also explain the lack of early improvement in LA function that we observed in our research.

Interestingly, in our study, mitral regurgitation severity reduced significantly after CRT, but no longer correlated to LAVIs, despite statistically significant correlations before CRT. Considering these facts, we hypothesized that, in our study group, reductions in LAVIs after CRT did not depend much on intrinsic myocardial changes, and did not correlate linearly with the severity of mitral regurgitation, but must have been triggered by another acutely modified parameter. Accordingly, we tested the correlations between LAVIs and atrio-ventricular dyssynchrony, as assessed by the diastolic filling/RR interval ratio, which were statistically significant, suggesting that this parameter is more likely to influence LAVIs in acute settings than the decreased severity of mitral regurgitation. This is an important finding that seems to suggest the importance of prolonging the diastolic filling time by reducing the heart rate with medication and adjusting atrio-ventricular delays while preserving a favourable transmitral flow pattern, without E and A wave fusion and truncated A waves. Such an approach would contribute to reducing LAVIs, thus improving outcomes in CRT patients. Moreover, the results of our study seem to suggest that the assessment of LA volumes by conventional echocardiography could be a simple and widely available technique for assessing the early impact of CRT.

The main limitation of the study is the low number of enrolled patients and the short follow-up time. Also, atrial strain quantification would have been of interest, but the appropriate software was not available and measurements could not be performed. All recruited patients were clinical responders to CRT and had echocardiographic evidence of early LV reverse remodeling. As a consequence, we could not test the ability of the studied parameters for predicting the response to CRT. Further research, on a larger number of patients that would also include non-responders, could endorse or reject the study of LA size and function variations within days after the implant procedure.

Conclusions

The results of the current study suggest that, within days after the implant procedure, LAVIs may undergo significant changes, and that these changes are correlated to the reduction in atrio-ventricular dyssynchrony, rather than the diastolic function, which remains unchanged, and the acute reduction in mitral regurgitation.

Conflicts of interest: no competing interests.

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