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Predictive value of left atrial remodeling for response to cardiac resynchronization therapy

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Keywords

heart failure, cardiac resynchronization therapy, left atrial remodeling, left atrial strain, left ventricular reverse remodeling

Abstract

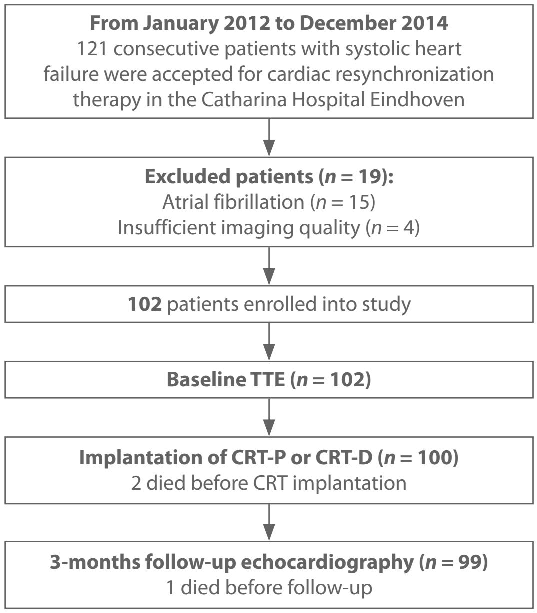
Aim: Response to cardiac resynchronization therapy varies significantly among patients, with one third of them failing to demonstrate left ventricular reverse remodeling after cardiac resynchronization therapy. Left atrial size and function is increasingly recognized as a marker of disease severity in the heart failure population. The aim of this study was to evaluate whether echocardiographic left atrial indices predict left ventricular reverse remodeling after cardiac resynchronization therapy. **Materials and methods:** Ninety-nine cardiac resynchronization therapy candidates were prospectively included in the study and underwent echocardiography before and 3-months after cardiac resynchronization therapy implantation. Cardiac resynchronization therapy response was defined as a 15% relative reduction in left ventricular end-systolic volume. Indexed left atrial volume, left atrial reservoir strain, left ventricular end-diastolic volume, and left ventricular ejection fraction along with other known predictors of cardiac resynchronization therapy response (gender, etiology of heart failure, presence of typical left bundle branch block pattern, QRS duration >150 ms) were included in a multivariate logistic regression model to identify predictors for cardiac resynchronization therapy response. **Results:** Cardiac resynchronization therapy response occurred in $n = 63$ (64%) patients. The presence of a typical left bundle branch block (OR 4.2, 95 CI: 1.4–12.1, $p = 0.009$), QRS duration >150 ms (OR 4.2, 95 CI: 1.4–11.0, $p = 0.029$), and left atrial volume index (OR: 0.6, 95 CI: 0.4–0.9, $p = 0.012$) remained the only significant predictors for cardiac resynchronization therapy response after three months. None of the baseline left ventricular parameters showed an independent predictive value. **Conclusion:** Left atrial size at baseline is an independent predictor and is inversely proportional to left ventricular volumetric reverse remodeling in cardiac resynchronization therapy candidates.

Introduction

Cardiac resynchronization therapy (CRT) is an important therapy for patients with heart failure (HF), reduced left ventricular (LV) function, and a wide QRS complex[1]. By restoring electrical synchrony, CRT leads to an improvement in both cardiac size and function, so-called reverse remodeling[2]. The induced beneficial process of LV reverse remodeling by CRT has been identified as the primary mechanism of reduced mortality, higher exercise capacity, and reduced hospitalization rates in this population[3,4].

Unfortunately, response to CRT varies significantly among patients, with one third of them failing to demonstrate LV reverse remodeling after CRT[5]. The variability of individual response to CRT warrants improved patient selection.

Recently, there has been a growing interest in left atrial (LA) volume and function in HF patients, as these are a known marker of disease severity in this population. The LA remodels due to chronically elevated high filling pressure over time. LA remodeling is a complex process that is defined as a persistent change in LA size (LA structural remodeling) and/or function (LA functional remodeling). Previously, a substudy of the MADIT-CRT trial showed that a smaller baseline LA volume is independently associated with response to CRT[6]. This highlights the importance that an insight in LA volume and function is pivotal in this population. Speckle-tracking echocardiography allows a more comprehensive analysis of LA function that could be of additional value to predict CRT response. Therefore, the objective of the present study was to evaluate the predictive value of LA structural (LA volume) and functional (LA reservoir strain) remodeling to LV CRT response.



TTE – transthoracic echocardiogram; CRT-P – biventricular pacemaker only; CRT-D – biventricular pacemaker with defibrillator

Fig. 1. *Flowchart of patient selection*

Materials and methods

Study design

This was a prospective, non-randomized, observational, single-center study. The study was conducted following the Good Clinical Practice guidelines of the Declaration of Helsinki and was approved by the Regional Ethical Committee. All subjects gave written informed consent.

Population

The study population consisted of patients with systolic heart failure who were referred for cardiac resynchronization therapy (CRT) to the Catharina Hospital (Eindhoven, the Netherlands) between January 2012 and December 2014[7]. All patients received optimized medical therapy before CRT implantation. Patients with insufficient image quality and/or atrial fibrillation were excluded. Functional status was assessed by the estimation of the New York Heart Association (NYHA) functional class.

Implantation technique

Standard techniques were used to implant the CRT device. Three transvenous pacing leads were inserted: one in right atrium, another in the high interventricular septum or right ventricular apex, and the coronary sinus lead was positioned near the LV free wall through a coronary sinus tributary vein. The pacing leads were connected to a dual-chamber biventricular device with programmable interventricular delay. The device was programmed in the DDD mode and the atrio-ventricular (AV) delay was adjusted during simultaneous pacing.

Echocardiographic evaluation

Echocardiograms were obtained before and 3 months after CRT implantation and analyzed by two experienced readers. For the recording, an iE33 ultrasound scanner equipped with a S1-1 transducer (Philips Healthcare, Andover, MA, USA) was used. Standard 2D- and Doppler-echocardiographic measurements were performed following ASE/EACVI guidelines, including both LV end-systolic and end-diastolic volume (LVESV and LVEDV)[8]. LV ejection fraction (LVEF) was calculated using the modified biplane Simpson's rule. Maximum LA volume indexed to body surface area (LAVI) was calculated by the biplane method of disks at end-systole. Commercially available software (QLAB 13, Philips Healthcare, Eindhoven, the Netherlands) was used to measure LA reservoir strain (LASr) on an apical four- and two-chamber views of the LA with a stable ECG recording and frame rated >60 frames per second[9,10]. The LA endocardial border was automatically drawn followed by manual adjustment if required. The zero strain reference was set at end-diastole in order to determine LASr[9].

Definition of LV reverse remodeling

The objective of this study was to identify predictors of LV reverse remodeling 3 months after CRT delivery. *LV reverse remodeling* was defined as a relative reduction in LVESV of ≥15%, in concordance with previous trials[11,12].

Predictors for LV reverse remodeling

Both LA and LV baseline parameters were tested as potential predictors of LV reverse remodeling after CRT[13], together with the following baseline parameters: gender, HF etiology, presence of typical LBBB pattern, and QRS duration[13]. For LA *structural remodeling* and LA *functional remodeling*, we selected baseline LA volume index (LAVI) and baseline LA reservoir strain (LASr), respectively. For *LV remodeling* baseline LVEDV and LVEF were used.

Tab. 1. *Patient characteristics*

	Total group (*n* = 99)	LV responders (*n* = 63)	LV non-responders (*n* = 36)	*P*-value
Demographics				
Age (yr)	70 (65–76)	70 (64–74)	71 (65–76)	0.64
Male	63 (64%)	35 (56%)	28 (78%)	0.03
Medical history				
Ischemic heart failure	51 (52%)	29 (46%)	22 (61%)	0.21
Hypertension	32 (32%)	23 (37%)	9 (25%)	0.27
Diabetes Mellitus	23 (23%)	13 (21%)	10 (28%)	0.50
COPD	7 (7%)	4 (6%)	3 (8%)	0.70
Chronic kidney disease (MDRD <30)	4 (4%)	2 (3%)	2 (6%)	0.62
ECG characteristics				
LBBB	72 (73%)	54 (86%)	18 (50%)	<0.001
QRSD [ms]	166 ± 22	167 ± 16	163 ± 29	0.37
QRSD >150 ms	78 (79%)	54 (86%)	24 (67%)	0.04
Laboratory parameters				
MDRD [mL/min/1.73 m^2]	58 (45–61)	60 (50–61)	53 (43–60)	0.07
NT-proBNP (pg/mL)	1438 (626–2791)	1226 (567–2009)	1776 (1184–3298)	0.04
Echocardiographic parameters				
LVEDV (mL/m^2)	117 (107–138)	115 (100–136)	122 (109–142)	0.06
LVESV (mL/m^2)	87 (71–106)	84 (70–103)	89 (75–108)	0.25
LVEF (%)	28 ± 8	28 ± 7	27 ± 8	0.32
LAVI (mL/m^2)	40 (31–52)	36 (28–47)	45 (37–60)	<0.001
LASr (%)	16 (10–21)	18 (12–22)	12 (8–17)	<0.005
Mitral regurgitation ≥ moderate (n, %)	34 (34%)	18 (29%)	16 (44%)	0.13
NYHA functional class				
II / III / IV	35/62/2 (35%/63%/2%)	25/37/1 (40%/59%/2%)	10/25/1 (28%/69%/3%)	0.37
Heart failure medication				
Beta-blocker	85 (86%)	55 (87%)	30 (83%)	0.77
Renin-angiotensin system antagonist	89 (90%)	58 (92%)	31 (86%)	0.49
Mineralocorticoid antagonist	36 (36%)	20 (32%)	16 (44%)	0.28
Lis diuretics	59 (60%)	32 (51%)	27 (75%)	0.02

COPD – chronic obstructive pulmonary diseases; LBBB – left bundle branch block; MDRD – modification of diet in renal disease; NT-pro BNP – N-terminal brain natriuretic peptide; LVEDV – left ventricular end-diastolic volume; LVESV – left ventricular end-systolic volume; LVEF – left ventricular ejection fraction; LAVI – left atrial volume index; LASr – left atrial reservoir strain; NYHA = New York Heart Association; IQR – indicates interquartile range

Statistical analysis

Data for continuous variables are presented as mean ± standard deviation (SD) or as median with interquartile range (IQR) in the case of skewed distribution. Categorical variables are presented as numbers (percentages). Mann-Whitney U test was used to compare medians between survivors and non-survivors. The paired t-test or Wilcoxon signed rank test was used to evaluate differences in continuous variables between baseline and 3-month follow-up. A two-sided p-value of less than 0.05 was considered to indicate statistical significance. The significance of predictors for the occurrence of CRT-induced LV response was evaluated using the univariate and multivariate logistic regression model. Backward stepwise selection based on the likelihood ratio was used in the multivariate analysis to reduce the number of predictors. Multicollinearity was detected using variance inflation factors. Odds ratios (ORs) with 95% confidence intervals (95 CI) were used to quantify the effect of the individual predictors. ORs not including 1 were considered significant. All analyses were performed using SPSS version 25 (IBM Corporation, Armonk, New York).

Results

Patient selection

The study population consisted of 121 consecutive patients with systolic heart failure accepted for CRT. Nineteen patients were excluded because of atrial fibrillation (n = 15) or insufficient imaging quality (n = 4). Two patients died before CRT implantation and one patient died before the 3-month follow-up echocardiography. The final study population consisted of 99 patients in whom LV reverse remodeling could be determined (Fig. 1).

Baseline characteristics

Table 1 shows patient characteristics of the study population. Heart failure was of ischemic origin in 51 (52%) patients. Patients were predominantly male (n = 63, 64%) with a median age of 70 (65–76) years. Main comorbidities were hypertension (n = 32, 32%) and diabetes (n = 23,

Tab. 2. *Cox proportional hazard regression analysis*

	Univariate analysis		Multivariate analysis	
Variables	**OR (95 CI)**	***P*-value**	**OR**	***P*-value**
Female	2.8 (1.1–7.1)	0.03	–	
Ischemic etiology of heart failure	0.5 (0.2–1.2)	0.15	–	
Electrocardiographic parameter				
LBBB	6.0 (2.3–15.7)	<0.01	4.2 (1.4–12.1)	0.009
QRSD >150 ms	3.0 (1.1–8.1)	0.03	4.2 (1.4–11.0)	0.029
Echocardiographic parameter				
LVEDV (per 20 mL/m²)	0.9 (0.7–1.1)	0.35		
LVEF (per 5%)	1.1 (0.9–1.5)	0.31		
LAVI (per 10 mL)	0.6 (0.4–0.8)	0.001	0.6 (0.4–0.9)	0.012
LASr (per 10%)	2.5 (1.3–4.7)	0.005	-	
LBBB – left bundle branch block; LVEF – left ventricular ejection fraction; LVEDV – left ventricular end-diastolic volume; LAVI – left atrial volume index; LASr – left atrial reservoir strain;				

23%). The intraventricular conduction delay was most commonly based on a left bundle branch block (n = 72, 73%) with a mean QRS duration of 166 ± 22 ms. More than half of the patients (63%) were reported as NYHA class III at baseline. At baseline, median LVESV was 87 (71–106) mL/m^2, LVEF 28 ± 8%, and LAVI 40 (31–52) mL/m^2. The majority of patients were treated with beta blockers (86%), renin-angiotensin system antagonists (90%), and to a lesser extent with mineralocorticoid antagonist (36%) and diuretics (60%).

LV reverse remodeling after 3 months CRT

At 3 months, 63 patients (64%) were considered as responders to CRT with a relative reduction in LVESV of ≥15%. The LV volumetric responders showed also a significant improvement in LVEF (28 to 42%; p <0.01). No significant change in LVEDV and LVEF was observed in the group of LV volumetric non-responders (Δ LVESV <15%).

Predictors for LV reverse remodeling

The prevalence of LBBB and QRS duration >150 milliseconds were significantly higher in LV responders compared to the non-LV responders (Tab. 1). LAVI, as a measure of baseline LA structural remodeling, was significantly higher in LV non-responders (45 versus 36 mL/m^2; p <0.01). LASr at baseline was significantly lower (12 versus 18%; p <0.01). Baseline LVEF was comparable (p = 0.32).

Both LAVI and LAS_r were associated with LV reverse remodeling in unadjusted analysis. In multivariate analysis, LAVI was the only echocardiographic variable to remain significant (Tab. 2). Figure 2 shows the proportion of LV responders in the study population subdivided by tertiles of LAVI. Small LA size at baseline (LAVI <34 mL/m^2) is associated with a high proportion of CRT responders of 81% in contrast to severely dilated LA at baseline (LAVI >48 mL/m^2) with only 48% response rate. Figure 3 shows the correlation between relative change of LVESV and baseline LAVI (Panel A) and LASr (Panel B).

Discussion

In our study, both typical LBBB and wide QRS duration were associated with CRT response; both well-known predictors for CRT volumetric response[13]. The important finding in our study was that LAVI was an independent predictor and was inversely proportional to LV volumetric response after CRT. This is in line with previous CRT study. The MADIT investigators have already shown that a smaller LA size is a strong predictor of CRT response[14]. Notably, the important association between LAVI and CRT response was maintained after adjustment for baseline LV end-diastolic volume and function, whereas the latter parameters were not shown to be of independent predictive value.

There is increasing evidence of the importance of LA function incremental to atrial dilation in HF patients. LA strain analysis is a relatively new, robust and feasible technique

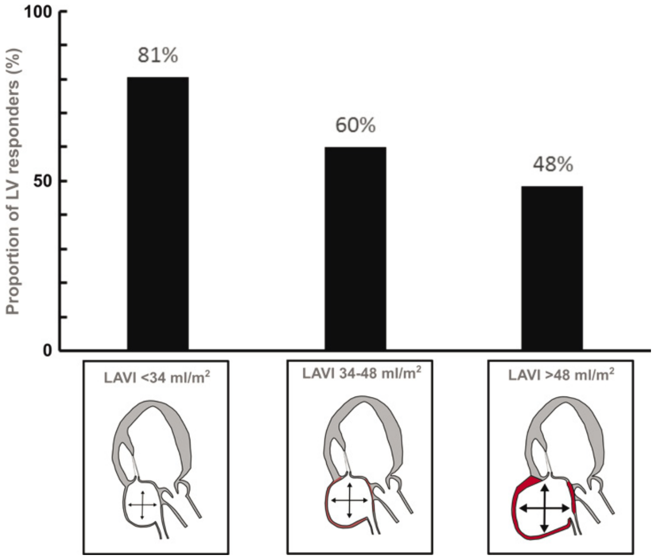


Fig. 2. *Proportion of LV responders in study population subdivided by tertiles of LAVI. LV reverse remodeling was defined as a relative reduction in LV end-systolic volume of ≥15%. LAVI – left atrial volume index*

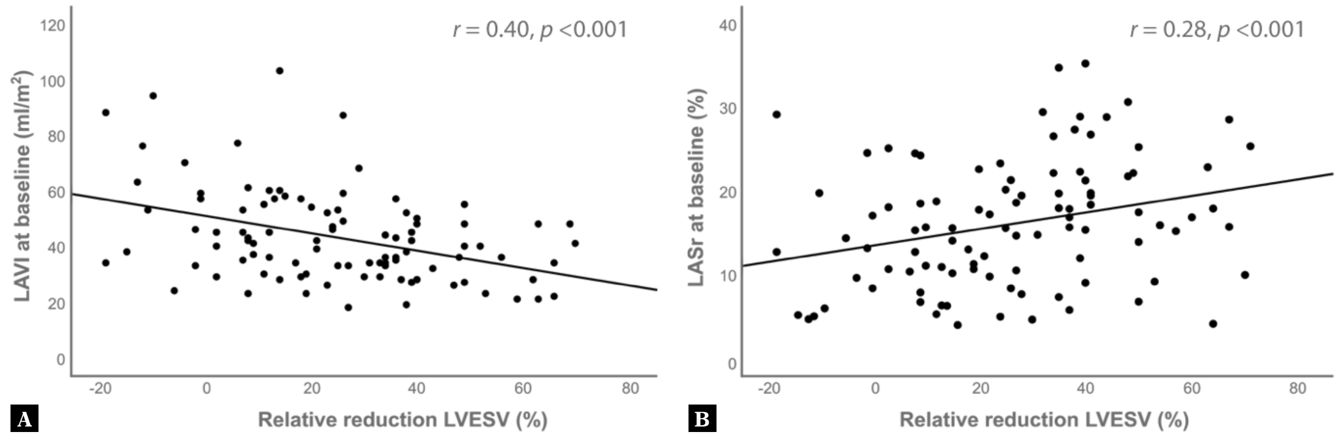


Fig. 3. *Correlation between relative reduction of LVESV and LAVI (Panel A) and LASr (Panel B). LVESV – left ventricular end-diastolic volume; LAVI – left atrial volume index; LASr – left atrial reservoir strain*

for quantifying LA function[9]. In this study, we have used a prospective single-center CRT database from 2012–2014 to evaluate the predictive value of this new echo parameter. In our study, LA reservoir strain (LASr) was not associated with LV reverse remodeling in a multivariate analysis. Remarkably, this observation is not in line with a previous study by Feneon *et al*.[15] In this small study of 79 patients, LASr was an independent predictor for LV response. A larger prospective multicenter study by Galli *et al*.[16] also provided evidence that LASr is an independent predictor (p = 0.049). However, the correlation between LASr and LV response was weak (r = –0.27, p <0.001) as in our study (r = –0.28, p <0.001). Nevertheless, the results of these studies underscore the importance of assessing left atrial condition in CRT candidates, in agreement with our results. Improved patient selection will reduce the relatively high costs associated with CRT treatment.

Study limitations

This study covered a relatively small number of patients in a single center. Therefore, the results need validation in larger external cohorts. Secondly, follow-up measurements of LVESV at 6 and 12 months were not performed. However, most LV reverse remodeling will occur within 3 months and will adequately identify responders and non-responders to CRT[17]. Thirdly, patients with atrial fibrillation were excluded from this study, and the predictive value of LAVI in this specific group of HF patients deserves further investigation. Intervendor variability of LASr quantification remains an issue and can be a possible explanation for the difference in the outcomes with previous studies.

Conclusions

LA size at baseline is an independent predictor and is inversely proportional to LV volumetric reverse remodeling in CRT candidates.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Author contributions

Original concept of study: SB, PH. Writing of manuscript: SB, TM, PH. Analysis and interpretation of data: SB, TM. Critical review of manuscript: SB, FP, LD, PH.

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