Multimodality imaging in the characterization and risk-stratification of cardiac disease and CRT recipients

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Left ventricular remodeling and change in left ventricular global longitudinal strain after cardiac resynchronization therapy: prognostic implications

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) has the ability to reduce left ventricular, end-systolic volume (LVESV). A decrease of ≥15% is commonly defined as a CRT response. CRT can also improve LV global longitudinal strain (GLS). Changes in LVESV and LV GLS are individually associated with outcome post-CRT. The objective of the current study was to investigate how often improvement in both LVESV and LV GLS coincides and if this response has a different prognostic implication than an improvement in either LVESV or LV GLS alone, and when compared to no improvement in either LVESV or LV GLS.

Methods: Baseline and 6-month echocardiograms were analyzed from CRT recipients with heart failure. LV reverse remodeling was defined as a ≥15% reduction in LVESV at 6 months post-CRT. A ≥5% absolute improvement in LV GLS was defined as a change in LV GLS.

Results: 1 185 patients were included (mean age 65±10 years, 73% male). Patients with an improvement in LVESV and LV GLS (n=131, 11.1%) had significantly lower all-cause mortality, compared to other groups. On multivariable analysis, an improvement in both LVESV and LV GLS (hazard ratio 0.47; 95% confidence interval 0.31-0.71; P<0.001) or an improvement in either LVESV or LV GLS (hazard ratio 0.57; 95% confidence interval 0.47-0.71; P<0.001) was independently associated with a better prognosis, compared to no improvement in either LVESV or LV GLS.

Conclusions: Changes in LVESV and LV GLS reflect different mechanisms of CRT response, which may not always be present in the same patient. Both improvement in LVESV and LV GLS occurred in 11.1% of patients. Either a reduction in LVESV and/or an improvement in LV GLS at 6 months post-CRT, is independently associated with improved long-term prognosis, compared to no change in both LVESV and LV GLS. These observations support the use of LV GLS as a meaningful parameter in defining CRT response, in addition to the more commonly used definition of a change in LVESV.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is indicated for heart failure (HF) patients who remain symptomatic despite receiving adequate medical therapy (New York Heart Association (NYHA) functional class II-III and ambulatory IV), together with a wide QRS complex (≥130 ms) and a left ventricular ejection fraction (LVEF) ≤35%.[1,2] In appropriately selected candidates, CRT alleviates symptoms, induces LV reverse remodeling, improves LV function and decreases mortality.[1]

The ability of CRT to cause LV reverse remodeling, i.e. to reduce the LV end-systolic volume (LVESV), has been extensively documented.[3-6] This is usually measured at 6 months post-implant. In addition, the degree of reduction in LVESV by CRT has been linked to long-term outcome.[7] Myocardial strain imaging quantifies active myocardial deformation, and global LV function is most commonly reported as global longitudinal strain (GLS). CRT can improve LV GLS, which also translates into an improved long-term outcome.[8,9] From a prognostic perspective, it would be important to know to what extent these early changes (a reduction in LVESV and an improvement in LV GLS) are predictive of long-term survival. Accordingly, we have evaluated the outcome of CRT recipients with early (6 months post-implant) improvement in both these parameters (LVESV and LV GLS), compared to the outcome of patients without early (6 months) improvement, as well as of CRT recipients with either improvement in LVESV or improvement in LV GLS, but not in both parameters.

METHODS

Study population

Clinical and echocardiographic data of HF patients who received CRT according to prevailing guideline recommendations were included from an ongoing, single-center registry.[1,10] For this analysis, only patients who underwent transthoracic echocardiography at baseline and at 6 months follow-up after CRT implantation were evaluated. Ischemic etiology of HF was defined by the presence of significant coronary artery disease. The NYHA functional class was assessed in all patients, and a clinical response to CRT was defined as a ≥1 NYHA class improvement at 6 months after CRT. The quality of life was evaluated with the Minnesota Living with Heart Failure Questionnaire,[11] and if feasible, a 6-minute walk test was performed.[12]

Echocardiographic data acquisition

Transthoracic echocardiograms were performed on all patients in the left lateral decubitus position with a commercially available echocardiographic system (VIVID 7 or E9, General Electric Healthcare, Horten, Norway). Data were acquired with 3.5 MHz or M5S transducers – adjusting the depth and gain settings when required. ECG-triggered, M-mode, 2-dimensional and Doppler data were collected and stored in digital format for off-line analysis (EchoPac 113, General Electric Healthcare, Horten, Norway). LVESV and LV end-diastolic volume (LVEDV) were mea-

sured on 2-dimensional 2- and 4-chamber apical views following Simpson's method and LVEF was then calculated.[13] LV GLS was measured from standard apical views (long-axis, 2-chamber and 4-chamber) using speckle tracking echocardiography.[14] The inter- and intra-observer agreement for LV GLS measurement in this population have previously been described.[15] The inter- and intra-observer variability of LVESV and LV GLS measurement were assessed calculating the intra-class correlation coefficient (ICC) for both measures on 25 randomly selected patients. The ICC for inter- and intra-observer variability of LVESV were 0.91 (95% CI: 0.76-0.96, P<0.001) and 0.98 (95% CI: 0.96-0.99, P<0.001), respectively. The bias and 95% limits of agreement for inter-observer variability of LVESV were -15.2 ml and -71.5 to 41.1 ml, respectively, whereas the bias and 95% limits of agreement for intra-observer variability of LVESV were 0.8 ml and -27.7 to 29.4 ml, respectively. The ICC for inter- and intra-observer variability of LV GLS were 0.92 (95% CI: 0.84-0.97, P<0.001) and 0.97 (95% CI: 0.89-0.99, P<0.001), respectively. The bias and 95% limits of agreement for inter-observer variability of LV GLS were 0.1% and -2.7 to 2.9%, compared to the bias and 95% limits of agreement for intra-observer variability of LV GLS, which were -0.5% and -2.1 to 1.1%.

CRT implantation

Placement of the right atrial and ventricular leads was performed via a standard approach (subclavian or cephalic vein). A coronary sinus venogram was acquired prior to LV lead implantation. An 8 Fr guiding catheter was subsequently used for insertion of the LV pacing lead into the coronary sinus, and for positioning in a (preferred) posterior/posterolateral vein. A connection was established between all leads and a dual-chamber, biventricular CRT device. In most patients (94%), a CRT device with defibrillator function was implanted, while 6% received a CRT device without defibrillator functionality. Patients were followed up with regular intervals at the HF outpatient clinic, at which time device function was checked. The atrioventricular and inter-ventricular delays were empirically set at 120-140 ms and 0 ms, respectively. Optimization of CRT devices was performed during follow-up, and at the discretion of the treating physician.

Definitions of early (6 months) CRT response

The definition of an echocardiographic response to CRT was based on the occurrence of LV reverse remodeling and improvement in LV GLS at 6 months of follow-up. LV reverse remodeling was defined as a reduction of ≥15% in the LVESV.[16] The cut-off value of clinically meaningful LV GLS improvement after CRT has not been previously established. An absolute improvement of 5% in LV GLS was chosen as a threshold representing a substantial GLS response (Figure 1).

Statistical analysis

Means and standard deviations were used to present continuous data, while numbers and percentages were used to present categorical data. Continuous variables were compared with one-way analysis of variance (ANOVA), while χ^2 and Fisher's exact tests with post-hoc analysis of

subgroups were employed for comparison of categorical data (as appropriate). Survival analysis was conducted with the Kaplan-Meier method, and the effect of different variables on event-free survival was examined with a Cox proportional hazards model. In order to evaluate the incremental value of LV GLS over a reduction in LVESV for outcome, we performed likelihood ratio testing. All 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.

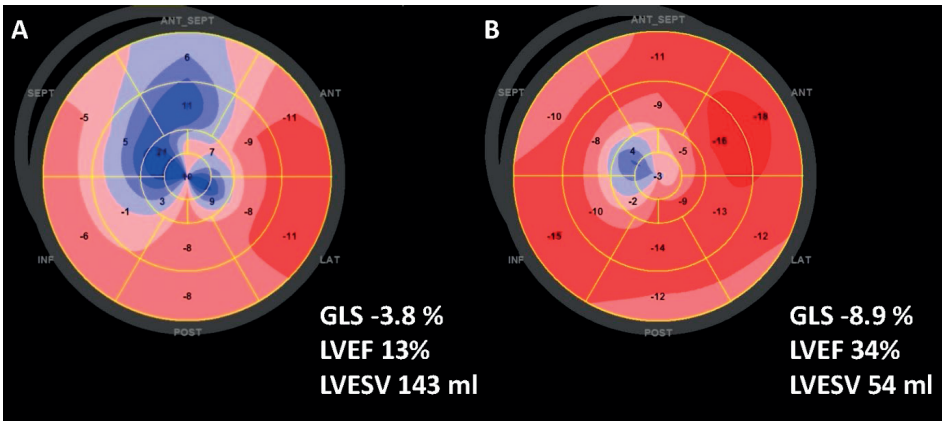


Figure 1: Parametric maps of left ventricular (LV) global longitudinal strain (GLS) for a cardiac resynchronization therapy (CRT) recipient with a substantial improvement in LV GLS. A) LV GLS parametric map before implantation of CRT, and B) the same patient after 6 months of CRT. LV segments coded in shades of blue denote elongation during systole, vs. LV segments coded in red, which indicate systolic shortening. LVEF: LV ejection fraction, LVESV: LV end-systolic volume.

RESULTS

Baseline patient characteristics

A total of 1 185 patients (mean age 65±10 years, 73% male) with available echocardiographic data at baseline and 6 months' follow-up were included (Table 1). Ischemic etiology was present in 56% of patients. The mean LVEF of the overall population was 27±8%.

Changes in LVESV and LV GLS

The mean reduction in LVESV after 6 months of CRT was 15.4±24.3 ml for the overall population (Figure 2), while LV reverse remodeling was observed in 674 patients (56.9%). The mean (absolute) change in LV GLS for the overall population after 6 months of CRT was 1.0±3.5% (Figure 2). A ≥5% absolute improvement in LV GLS was observed in 148 (12.5%) patients. Improvement in both LVESV and LV GLS was noted in 131 (11.1%) of CRT recipients, compared to 469 (39.6%) who did not improve either their LVESV or GLS. In 585 (49.4%) patients, an improvement was seen in either LVESV or GLS, but not in both.

Characteristics of patients according to CRT response pattern

Table 1 compares the baseline characteristics of patients, divided according to the CRT response pattern. Those who improved both their LVESV and LV GLS, demonstrated a longer baseline QRS duration, compared to patients who either did not improve their LVESV or LV GLS, or who showed improvement in only LVESV or LV GLS. CRT recipients with neither an improvement in LVESV nor in LV GLS, were more frequently male and more commonly had an ischemic etiology of HF. In addition, patients not manifesting a decrease in LVESV or an improvement in LV GLS, had more renal dysfunction than those with an improvement in both LVESV and LV GLS.

Table 1: Baseline characteristics.

	≥15% ↓LVESV and ≥5% ↓GLS (n=131)	≥15% ↓LVESV or ≥5% ↓GLS (n=585)	<15% ↓LVESV and <5% ↓GLS (n=469)	Overall population (n = 1 185)
Age (years)	66.6±10.2	65.7±10.2	64.2±10.5	65.2±10.3
Male gender, n (%)	79 (60.3)	419 (71.6)†	363 (77.4)*	861 (72.7)
Ischemic etiology, n (%)	50 (38.2)	317 (54.2)*	298 (63.5)*	665 (56.1)
LBBB, n (%)	58 (44.3)	284 (48.5)	225 (48.0)	567 (47.8)
QRS duration at baseline (ms)	168.4±30.6	155.8±35.5*†	149.7±33.8*	154.6±34.8
Heart rhythm, n (%)				
- Sinus rhythm	83 (63.4)	449 (76.8)*	353 (75.3)	885 (74.7)
- Paced	22 (16.8)	57 (9.7)	42 (9.0)*	121 (10.2)
- Atrial fibrillation	26 (19.8)	79 (13.5)*	74 (15.8)	179 (15.1)
NYHA class, n (%)				
- I	6 (4.6)	31 (5.3)	16 (3.4)	53 (4.5)
- II	33 (25.2)	154 (26.3)†	112 (23.9)	299 (25.2)
- III/IV	92 (70.2)	400 (68.4)	341 (72.7)	833 (70.3)
6 MWT (m)	354.7±110.6	332.8±120.2	327.5±122.1	332.8±120.2
QoL score	31.5±17.4	30.2±18.4†	34.6±20.2	32.1±19.1
Diabetes mellitus, n (%)	13 (10.0)	106 (18.1)	113 (24.1)	232 (19.6)
eGFR <60 ml/min/1.73 m^2, n (%)	33 (25.2)	225 (38.5)	184 (39.2)*	442 (37.3)
LVEF (%)	26.6±7.7	27.3±7.9	27.7±8.2	27.4±8.0
LVEDV (ml)	201.3±67.7	205.1±75.6	203.0±78.3	204.0±76.0
LVESV (ml)	149.7±58.6	151.7±65.9	149.4±67.2	150.7±65.7
LV GLS (%)	-6.0±2.9	-7.7±3.5*†	-7.2±3.3*	-7.3±3.4
Medication, n (%)				
- Diuretic	76 (58.0)	440 (75.2)	375 (80.0)*	891 (75.2)
- Digoxin	9 (6.9)	88 (15.0)*	71 (15.1)*	168 (14.2)
- β-blocker	77 (58.8)	423 (72.3)	333 (71.0)	833 (70.3)
- Mineralocorticoid antagonist	50 (38.2)	238 (40.7)	205 (43.7)	493 (41.6)
- ACE-inhibitor	94 (71.8)	500 (85.5)	400 (85.3)	994 (83.9)

Continuous variables are mean ± standard deviation. ACE: angiotensin-converting enzyme, eGFR: estimated glomerular filtration rate, GLS: global longitudinal strain, LBBB: left bundle branch block, LV: left ventricular, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, 6 MWT: 6-minute walk test, NYHA: New York Heart Association, QoL: quality of life. *P<0.05 vs. ≥15% ↓LVESV and ≥5% ↑GLS; †P<0.05 vs. <15% ↓LVESV and <5% ↑GLS.

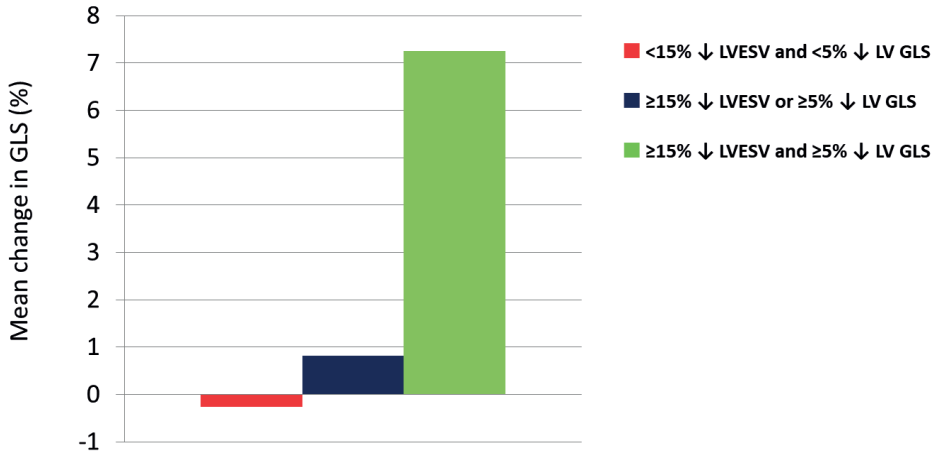


Figure 2A: Absolute changes in mean, left ventricular global longitudinal strain (GLS) from baseline to 6 months after cardiac resynchronization therapy (CRT), according to different categories of CRT response. LV: left ventricular, LVESV: left ventricular end-systolic volume.

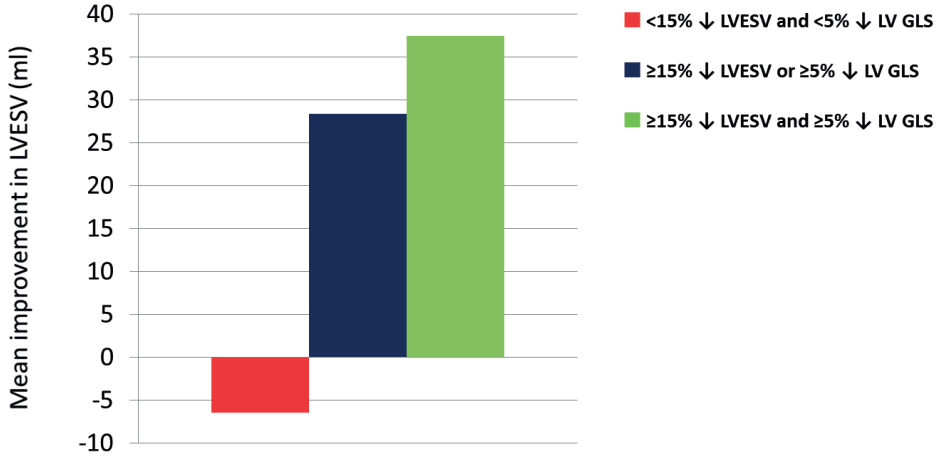
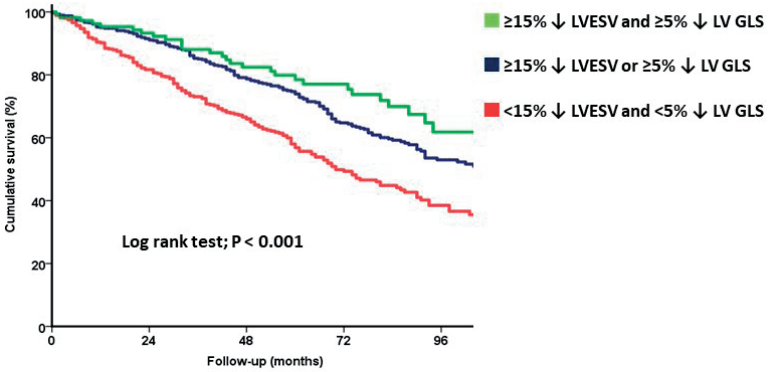


Figure 2B: Mean improvement in left ventricular end-systolic volume (LVESV) from baseline to 6 months after cardiac resynchronization therapy (CRT), according to different categories of CRT response. LV: left ventricular, GLS: global longitudinal strain.

Changes in LV GLS and LVESV before and after CRT implantation, according to different groups of CRT response, are summarized in Figure 2. A greater improvement of LV GLS was observed in those patients who improved in both LVESV and LV GLS, than in patients who improved only in terms of LVESV or LV GLS, or neither (P<0.001). The LVESV decreased more significantly in CRT recipients with LVESV and LV GLS improvement than in those recipients with an improvement in only LVESV or LV GLS, while LVESV increased in recipients without an improvement in either LVESV or LV GLS (P<0.001).

CRT response pattern and survival

After a median follow-up of 53 months (interquartile range 25-80 months), 323 (27%) patients died. CRT recipients in whom a reduction in LVESV was seen together with an improvement in LV GLS, had significantly better survival compared to those who improved either in LVESV or LV GLS, or did not improve in LVESV and LV GLS (log-rank test, P<0.001; Figure 3). In patients with an improved LVESV and LV GLS, the cumulative survival rates at 24, 48, 72 and 96 months of follow-up were 92, 82, 75 and 62%, respectively. The group that demonstrated an improvement in either LVESV or LV GLS but not both, showed slightly worse cumulative survival (91, 79, 64 and 53%, at 24, 48, 72 and 96 months of follow-up, respectively). In contrast, patients without improvement in LVESV or LV GLS had lower cumulative survival rates (81, 66, 49 and 37%, at 24, 48, 72 and 96 months of follow-up, respectively).



Number of patients at risk

≥15% ↓ LVESV and ≥5% ↓ LV GLS	131	91	68	46	12
≥15% ↓ LVESV or ≥5% ↓ LV GLS	585	457	332	198	85
<15% ↓ LVESV and <5% ↓ LV GLS	469	317	210	91	42

Figure 3: Kaplan-Meier survival curves for time to cumulative survival, according to different categories of cardiac resynchronization therapy (CRT) response. LV: left ventricular, LVESV: left ventricular end-systolic volume, GLS: global, longitudinal strain.

A Cox proportional hazards model was used to investigate the association between response to CRT at 6 months' follow-up and all-cause mortality, including as covariates, factors known to impact on mortality in HF (Table 2). On multivariable analysis, both a CRT response encompassing an improvement in LVESV and LV GLS (hazard ratio 0.47; 95% confidence interval (CI) 0.31-0.71; P<0.001) and a response characterized by an improvement in either LVESV or LV GLS (hazard ratio 0.57; 95% CI 0.47-0.71; P<0.001) were independently associated with better survival compared to patients without improvement in LVESV or LV GLS.

Table 2: Predictors of all-cause mortality risk, uni- and multivariate Cox proportional hazards models.

	Univariable analysis			Multivariable analysis		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Age at implantation (years)	1.04	1.03-1.05	<0.001	1.03	1.02-1.04	<0.001
Male gender	1.48	1.16-1.89	0.001	1.39	1.07-1.82	0.015
Body mass index (kg/m^2)	0.97	0.95-0.99	0.008	0.96	0.94-0.99	0.006
Diabetes mellitus	1.65	1.33-2.05	<0.001	1.37	1.08-1.74	0.010
Ischemic etiology of heart failure	1.55	1.27-1.89	<0.001	1.29	1.03-1.63	0.029
Diuretic use	1.75	1.33-2.31	<0.001	1.38	1.02-1.86	0.037
Hemoglobin (g/dL)	0.81	0.73-0.89	<0.001	0.92	0.82-1.02	0.114
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	2.55	2.11-3.08	<0.001	1.91	1.55-2.37	<0.001
Clinical response	0.84	0.69-1.01	0.068	0.86	0.70-1.05	0.132
QRS duration pre-implantation (ms)	1.00	1.00-1.01	0.108	1.00	1.00-1.01	0.165
Atrial fibrillation	1.75	1.38-2.22	<0.001	1.43	1.10-1.85	0.007
CRT response category						
<15% ↓LVESV and <5% ↓LV GLS	-	-	-	-	-	-
≥15% ↓LVESV or ≥5% ↓LV GLS	0.60	0.49-0.73	<0.001	0.57	0.47-0.71	<0.001
≥15% ↓LVESV and ≥5% ↓LV GLS	0.43	0.29-0.64	<0.001	0.47	0.31-0.71	<0.001

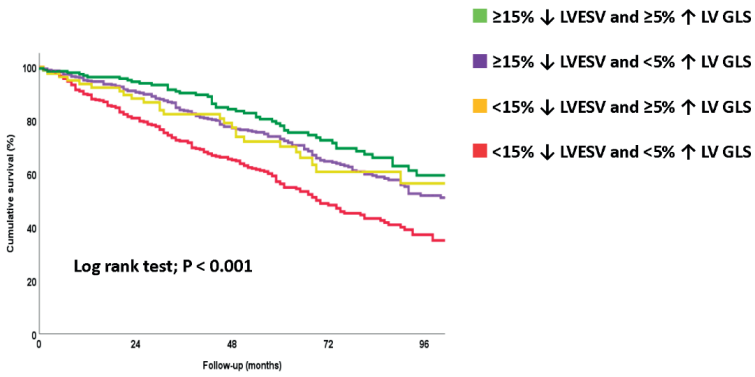
CI: confidence interval, CRT: cardiac resynchronization therapy, eGFR: estimated glomerular filtration rate, GLS: global longitudinal strain, HR: hazard ratio, LV: left ventricular, LVESV: left ventricular end-systolic volume.

In order to further stratify those responders who showed an improvement in either LVESV or LV GLS but not both, and to investigate the association with outcome, this group of patients was divided into two subcategories, i.e. those with a decrease in LVESV, and another with an improvement in LV GLS. Patients with an improved LV GLS but without a decrease in LVESV, demonstrated similar event rates to those with a reduced LVESV but no change in LV GLS (log-rank test P<0.001; Figure 4). An identical, multivariable model was constructed, and analyzed according to four patterns of CRT response, i.e. i) improvement in LVESV and LV GLS, ii) improvement in LVESV, iii) improvement in LV GLS, iv) neither improvement in LVESV nor improvement in LV GLS. The hazard ratios of patients with improved LV GLS but without a decrease in LVESV (hazard ratio 0.58; 95% CI 0.33-0.99; P=0.05) and those with a reduced LVESV but no improvement in LV GLS (hazard ratio 0.57; 95% CI 0.46-0.71; P<0.001) were similar, while the first group demonstrated a trend towards better survival, and the second group retained an independent association with outcome.

Incremental value of LV GLS

In order to evaluate the incremental value of an improvement in GLS over a reduction in LVESV for mortality, likelihood ratio testing was performed. The baseline model (model 1) comprised all risk factors which were included in the multivariable regression model, i.e.: age at implantation, male gender, body mass index, diabetes mellitus, ischemic etiology of heart failure, diuretic use, hemoglobin, renal dysfunction, clinical response, QRS duration pre-implantation and atrial fibrillation. Addition of a ≥15% decrease in LVESV to model 1, provided incremental

value (P<0.001; Figure 5). A third model, which included an improvement in GLS of ≥5%, was of further incremental value (P=0.039; Figure 5).



Number of patients at risk

≥15% ↓ LVESV and ≥5% ↑LV GLS	131	91	68	46	12
≥15% ↓ LVESV and <5% ↑LV GLS	536	425	309	188	79
<15% ↓ LVESV and ≥5% ↑LV GLS	49	32	23	10	6
<15% ↓ LVESV and <5% ↑LV GLS	469	317	210	91	42

Figure 4: Kaplan-Meier survival curves for time to cumulative survival. Survival is categorized according to four different cardiac resynchronization therapy (CRT) responses. LV: left ventricular, LVESV: left ventricular, end-systolic volume, GLS: global, longitudinal strain.

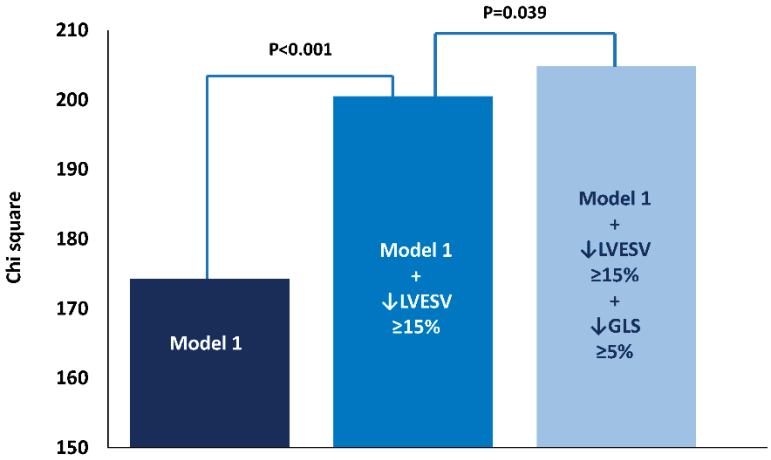


Figure 5: Likelihood ratio test. Bars represent the incremental value of a ≥15% decrease in left ventricular end-systolic volume (LVESV) and an improvement in LV global longitudinal strain (GLS) in addition to clinical risk factors (Model 1).

DISCUSSION

Improvement in both LVESV and LV GLS was noted in 11.1% of CRT recipients. Furthermore, it was demonstrated that CRT responses defined by i) improvement in both LVESV (reduction of ≥15%) and LV GLS (≥5% absolute improvement), or ii) improvement in either LVESV or LV GLS at 6 months after implantation, are independently associated with a better prognosis, compared to the absence of both an improvement in LVESV and LV GLS. Additionally, we showed that the groups of CRT recipients with either a decrease in LVESV or an increase in LV GLS, had a similar prognosis.

Decrease of LVESV after CRT

The response to CRT has been defined by a spectrum of both clinical (change in NYHA, change in 6-minute walking distance, change in quality of life (QoL) score) and echocardiographic (change in LVESV, change in LVEDV, change in LVEF and change in LV GLS) parameters.[7,8,17-19] The most frequently used definition of CRT response is a ≥15% reduction in LVESV at 6 months' follow-up, due to evidence supporting its prognostic implications.[7,17] The reduction which CRT causes in LVESV, has been documented in a number of landmark trials.[3-5] In the Multicenter InSync ICD Randomized Clinical Evaluation II (MIRACLE-ICD II) trial, the LVESV decreased by 14±57 ml in the control group, compared to 42±77 ml in the CRT group (P=0.01).[5] In the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study, indexed LVESV declined by 25.3±28.5 ml/m^2 in patients receiving CRT with a LBBB, compared to 1.7±25.8 ml/m^2 in a control group (P<0.0001).[3]

The degree of LV response at 6 months after CRT is also predictive of long-term outcome (log-rank test, P<0.001).[7] Since survival is a very robust measure of outcome, a reduction in the LVESV ≥15% has become the most accepted definition of CRT response. This definition, however, has certain limitations: change in LVESV reflects only the change in LV volume following CRT, and does not take into account whether it has improved exclusively by increasing the effective forward stroke volume. In addition, a CRT response defined only by a reduction in LVESV, does not reflect active deformation of the myocardium. Speckle tracking strain echocardiography can overcome this limitation by imaging active myocardial deformation. Global LV deformation, measured by speckle tracking strain echocardiography, is most commonly reported as LV GLS.[20]

Improvement of LV GLS after CRT

In 141 CRT recipients significant improvement in LV GLS (from -7.8±2.8% to -8.5±3.5%; P=0.01) was noted in responders (defined as a ≥15% reduction in LVESV) but not in non-responders.[9] Pouleur et al.[8] reported an improvement in LV GLS after CRT, which was associated with an improved outcome (24% reduction in death or HF for every 1% recovery in LV GLS) over the first 12 months of CRT. The mean change in LV GLS was 1.4±3.1% in this population.[8]

CRT response: LVESV and LV GLS

Inherent to the fact that a response to CRT is defined by means of different parameters, they may not all improve in the same patient, i.e. they may be discordant. Such discordant clinical and LV volumetric responses were witnessed in 440 CRT recipients.[21] The combined clinical endpoint of ≥1 point improvement in NYHA class and/or ≥15% improvement in the 6-minute walking test distance was compared to an echocardiographic, volumetric response defined as ≥15% reduction in the LVESV.[21] While a clinical response was recorded in 84% of patients, an echocardiographic response was seen in only 63%.[21] Discordance of CRT response parameters can be best investigated by the two measures which have been firmly linked to outcome after CRT, i.e. LVESV and LV GLS.

A discordant CRT response, defined as an improvement in LVESV or LV GLS, but not both, reflects different underlying mechanisms of CRT response. A reduction in LVESV without an improvement in LV GLS likely results from effective resynchronization of the LV by CRT, but without recruitment of contractile reserve. Contractile reserve describes the potential of poorly contractile, though viable, areas of myocardium, to improve their systolic function in response to CRT. The presence of contractile reserve in CRT candidates has been demonstrated with dobutamine stress-echocardiography, and it is associated with better event-free survival.[22-25] On the other hand, an improved LV GLS without a substantial change in LVESV can be attributed to the recruitment of contractile reserve. These two echocardiographic parameters (LVESV and LV GLS) therefore represent two different mechanisms of the LV response to CRT, and they do not always occur in the same patient concurrently.

The results of the present study indicate that no improvement in either LVESV or LV GLS, is significantly associated with a worse outcome, while improvement in both of these parameters or either one of them is associated with a survival benefit. Even though an improvement in LV GLS has previously been linked to an improved outcome, ≥15% reduction in the LVESV is a more commonly used definition of CRT response. Our results therefore support the use of an improvement in LV GLS as a useful parameter for the evaluation of a CRT response. Furthermore, the fact that CRT recipients with either a reduction in LVESV or an improvement in LV GLS had similar associations with outcome, provides insight into the different mechanisms of CRT response. Patients with an improvement in LV GLS but without a reduction in LVESV would have been classified as non-responders by the conventional definition of a CRT response, i.e. ≥15% reduction in LVESV, although they experience similar survival rates at 6 months as compared with patients with reduction in LVESV ≥15%. This observation further strengthens the importance of a change in LV GLS in defining CRT response. Furthermore, the incremental value of an improvement in LV GLS over a reduction of LVESV (in addition to clinical risk factors) for survival, lends additional support to the independent contribution of LV GLS in CRT response.

Study limitations

This was a retrospective, single-center study, which included patients who completed 6 months of follow-up. Patients who died during the first 6 months after CRT implantation could not be included, and could therefore have caused a selection bias. The measurement of LV GLS is not vendor-independent, and the threshold of LV GLS employed to define a response in the present study may not be generalizable to other patients in whom LV GLS was measured on a different vendor platform.[14]

CONCLUSIONS

Various clinical and echocardiographic parameters have been used to define a response to CRT, and due to different underlying mechanisms, they may not always be in agreement in the same patient. By observing the LV response to CRT in terms of two measures which have previously been associated with outcome, i.e. LVESV and LV GLS, we have demonstrated three different patterns of response, i.e. i) an improvement in both LVESV and LV GLS, ii) an improvement in either LVESV or LV GLS, but not both, iii) no improvement in either LVESV or LV GLS. An improvement in both LVESV and LV GLS, or an improvement in either LVESV or LV GLS, at 6 months after CRT, are associated with better long-term outcome, compared to no improvement in LVESV or LV GLS. These findings support the use of LV GLS as a meaningful parameter in defining CRT response, since it reflects a different aspect of LV response to CRT than a change in LVESV, and clearly impacts on long-term prognosis.

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