Chapter 13

Relative merits of left ventricular dyssynchrony, left ventricular lead position, and myocardial scar to predict long-term survival of ischemic heart failure patients undergoing cardiac resynchronization therapy

Delgado V, **van Bommel RJ**, Bertini M, Borleffs CJ, Marsan NA, Ng AC, Nucifora G, van de Veire NR, Ypenburg C, Boersma E, Holman ER, Schalij MJ, Bax JJ

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ABSTRACT

Background: The relative merits of left ventricular (LV) dyssynchrony, LV lead position and myocardial scar to predict long-term outcome after cardiac resynchronization therapy (CRT) remain unknown, and were evaluated in the current study.

Methods: In 397 ischemic heart failure patients, 2-dimensional speckle-tracking imaging was performed, with comprehensive assessment of LV radial dyssynchrony, identification of the segment with latest mechanical activation and detection of myocardial scar in the segment where the LV lead was positioned. For LV dyssynchrony, a cut-off value of 130 ms was used. Segments with <16.5% of radial strain in the region of the LV pacing lead were considered to have extensive myocardial scar (>50% transmurality, validated in a sub-group with contrast-enhanced magnetic resonance imaging). The LV lead position was derived from chest X-ray. Long-term follow-up included all-cause mortality and hospitalizations for heart failure.

Results: Mean baseline LV radial dyssynchrony was 133±98 ms. In 271 (68%) patients, the LV lead was placed at the latest activated segment (concordant LV lead position) and the mean value of peak radial strain at the targeted segment was 18.9±12.6%. Larger LV radial dyssynchrony at baseline was an independent predictor of superior long-term survival (hazard ratio [HR]: 0.995 per 1 ms increment, $p = 0.001$) whereas a discordant LV lead position (HR: 2.086, $p = 0.001$) and myocardial scar in the segment targeted by the LV lead (HR: 2.913, $p<0.001$) were independent predictors of worse outcome. Addition of these three parameters yielded incremental prognostic value over the combination of clinical parameters.

Conclusions: Baseline LV radial dyssynchrony, discordant LV lead position and myocardial scar in the region of the LV pacing lead were independent determinants of long-term prognosis in ischemic heart failure patients treated with CRT. Larger baseline LV dyssynchrony predicted superior long-term survival whereas discordant LV lead position and myocardial scar predicted worse outcome.

INTRODUCTION

Randomized controlled trials have demonstrated that cardiac resynchronization therapy (CRT) improves the clinical outcome of advanced heart failure patients with depressed left ventricular (LV) ejection fraction (<35%) and wide QRS complex (>120 ms).[1, 2] However, after application of the current selection criteria, a substantial percentage of patients does not benefit from CRT, particularly in patients with ischemic heart failure.[3-6] Consequently, multiple single-center studies have conducted extensive research to identify predictors of favorable mid-term outcome, defined as improvement in New York Heart Association (NYHA) functional class or reduction in LV end-systolic volume and improvement in LV ejection fraction at 6 months follow-up.[7] Baseline LV dyssynchrony, optimal LV lead position (in the latest mechanically activated region) and extent and location of myocardial scar have been proposed as determinants of mid-term outcome after CRT.[8-11] Only few studies however, have evaluated the determinants of long-term survival and morbidity reduction.[12, 13] Baseline LV dyssynchrony and optimal LV lead position appear important determinants of superior long-term outcome.[12, 13] In contrast, little is known about the impact of myocardial scar tissue on long-term outcome. More important, the relative merits of these three parameters (baseline LV dyssynchrony, LV lead position and myocardial scar) to predict long-term outcome remain unclear.

Currently, 2-dimensional speckle-tracking echocardiography can provide useful information on the presence of LV dyssynchrony, the location of the latest mechanically activated segment and on the presence and extent of scar tissue.[13-15] Accordingly, this imaging technique may be ideal to perform a comprehensive analysis (with focus on these three parameters) in advanced heart failure patients who are considered for CRT. The aim of the present study was to evaluate the relative merits of LV dyssynchrony, optimal LV lead position (in the latest activated segment) and presence of myocardial scar in the region where the LV pacing lead is placed to predict long-term outcome of patients with ischemic heart failure treated with CRT. Baseline LV dyssynchrony, latest activated segment and presence of myocardial scar were determined using a comprehensive 2-dimensional speckle-tracking analysis.

METHODS

Patient population

Between June 2000 and July 2008, a total of 397 patients with ischemic heart failure who received CRT at Leiden University Medical Center were included in the present study. Patients were selected for CRT according to the presence of depressed LV ejection fraction (≤35%), to-

gether with NYHA functional class III or IV and QRS duration on the surface electrocardiogram ≥120 ms. The criteria to define ischemic heart failure were: presence of significant coronary artery disease (≥50% stenosis in one or more of the major epicardial coronary arteries) and/or a history of myocardial infarction with electrocardiographic evidence of prior myocardial infarction. Patients with recent myocardial infarction (<3 months) or decompensated heart failure were excluded.

The clinical status was evaluated prior to CRT implantation (baseline) and at 6 months follow-up, and included the assessment of NYHA functional class, quality of life score according to the Minnesota Living with Heart Failure questionnaire and evaluation of exercise capacity using the 6-minute walk distance.[16, 17] Transthoracic 2-dimensional echocardiography was performed at baseline and 6 months follow-up. Favorable response to CRT was defined by a reduction in LV end-systolic volume ≥15% at follow-up.[18] All clinical and echocardiographic data were prospectively acquired.

Echocardiographic data

Patients were imaged in the left lateral decubitus position with a commercially available ultrasound system (Vivid-7, General Electric-Vingmed, Milwaukee, Wisconsin), equipped with a 3.5 MHz transducer. Standard 2-dimensional gray-scale and color-Doppler images triggered to the electrocardiogram were acquired in cine-loop format and transferred to a workstation for off-line analysis (EchoPac 7.0.0. GE Medical Systems, Horten, Norway).

Left ventricular end-diastolic and end-systolic volumes were assessed from the LV apical 2- and 4-chamber views and LV ejection fraction was derived according to the biplane Simpson's method.[19]

Comprehensive 2-dimensional speckle-tracking radial strain analysis

Two-dimensional speckle-tracking radial strain imaging has been previously used to assess LV mechanical activation, quantifying LV dyssynchrony and identifying the latest mechanically activated segment.[13, 15] In addition, 2-dimensional speckle-tracking radial strain imaging allows assessment of myocardial scar.[14] Accordingly, we performed a comprehensive 2-dimensional speckle-tracking radial strain analysis of the LV before CRT device implantation, including the assessment of LV dyssynchrony, the identification of the latest activated segment and the segmental value of radial strain.

LV dyssynchrony and latest activated segment.

Mid-ventricular short-axis LV images were selected to assess LV dyssynchrony and the latest activated segment. Standard 2-dimensional gray-scale images were acquired at an optimal frame rate to assure a reliable operation of the software (EchoPac 7.0.0, GE Medical Systems, Horten, Norway). By applying speckle-tracking radial strain analysis, time-radial strain curves of the 6 segments in which the LV is divided (anteroseptal, anterior, lateral, posterior, inferior and septal) were obtained. Time to peak radial strain was calculated for each segment and the latest activated segment was identified. A time delay between the anteroseptal and the posterior segments ≥130 ms defined the presence of substantial LV dyssynchrony (Figure 1).[15]

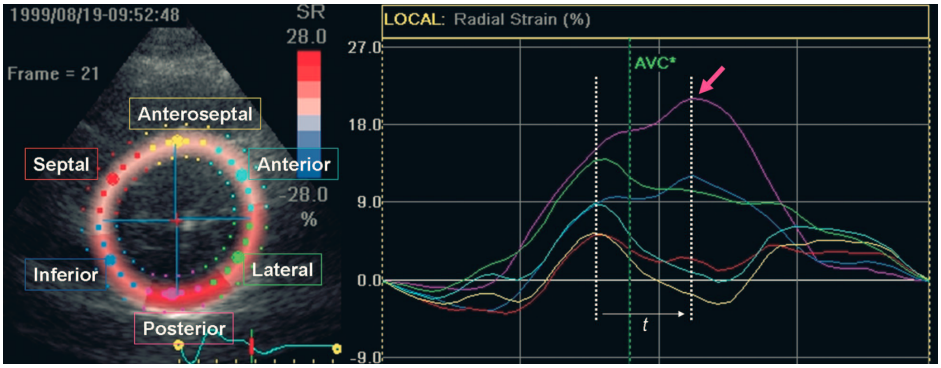

Figure 1. Assessment of LV radial dyssynchrony and latest mechanical activated segment by 2-dimensional speckle-tracking radial strain imaging. The mid-ventricular short-axis view of the left ventricle is divided in 6 segments and the time-radial strain curves are displayed. LV dyssynchrony is calculated as the time difference in peak radial strain between the anteroseptal and posterior segment. In addition, the latest activated segment is identified (posterior segment in this example, arrow).

Myocardial scar

Two-dimensional speckle-tracking radial strain analysis was additionally used to assess myocardial scar. From mid-ventricular short-axis images of the LV, peak radial strain was calculated for each of the 6 segments (Figure 2). Myocardial segments with a peak radial strain value <16.5% were considered to be scar segments, as previously validated.[14] To further validate this cut-off value in the present study population, contrast-enhanced magnetic resonance imaging data were analyzed and compared to 2-dimensional speckle-tracking radial strain data. Forty-three patients who underwent contrast-enhanced magnetic resonance imaging prior to CRT implantation were divided into two groups according to the percentage of hyper enhancement of the myocardial wall (≤50% or >50% of the wall).[20] Transmural myocardial

scar was defined by >50% hyper enhancement of the myocardial wall.[14, 20] Twenty-five (58%) patients showed >50% hyper enhancement in the area where the LV lead was placed whereas the remaining 18 patients showed ≤50% hyper enhancement. The mean radial strain value in segments with >50% hyper enhancement was significantly lower than in segments showing ≤50% hyper enhancement (11.7±1.3% vs. 21.3±2.4%, p<0.001). With receiver operating characteristic curve analysis a cut-off value of 16.5% radial strain identified transmural myocardial scar on contrast-enhanced magnetic resonance imaging, yielding an area under the curve of 0.83.

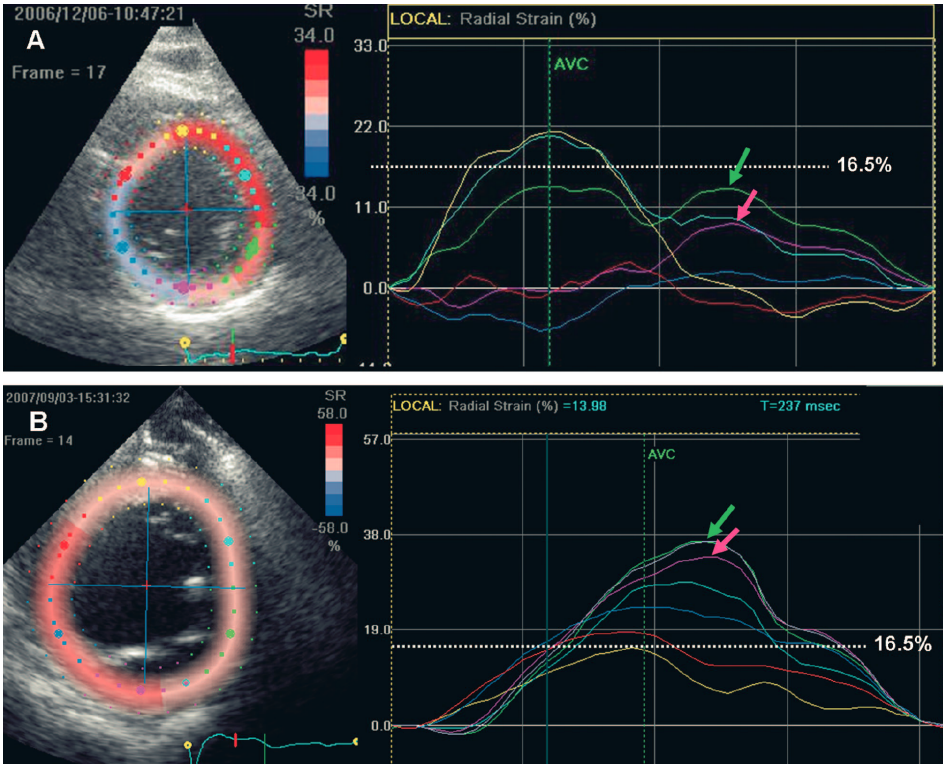

Figure 2. Assessment of segmental peak radial strain by 2-dimensional speckle-tracking imaging.
From the time-radial strain curves, peak radial strain can be quantified for each segment in which the left ventricle is divided. A pre-established cut-off value of 16.5% defines the presence of transmural myocardial scar (17). Panel A shows an example of a patient with myocardial scar in the latest activated segments (lateral and posterior segments: peak radial strain <16.5%) (arrows). In contrast, panel B shows an example of a patient without myocardial scar in the latest activated segments (peak radial strain ≥16.5%, arrows).

CRT device implantation

To insert the LV lead, first a coronary sinus venogram was obtained using a balloon catheter. Thereafter, an 8F guiding catheter was used to place the LV lead (Easytrak, Guidant Corporation, St. Paul, Minnesota; Attain, Medtronic Inc., Minneapolis, Minnesota; or Corox, Biotronik, Berlin) in the coronary sinus. The right atrial and ventricular leads were positioned conventionally. Finally, all leads were connected to a dual chamber biventricular CRT-device (Contak Renewal, Guidant Corporation; Insync III or Insync Sentry, Medtronic Inc; or Lumax, Biotronik, Berlin). The preferred position was a lateral or a posterolateral vein; the operator was blinded to the echocardiographic information concerning the site of latest mechanical activation.[13]

Assessment of LV lead position

After CRT device implantation, the LV lead position was confirmed from the chest X-ray as previously described.[21] Using the lateral views, LV lead positions were scored as anterior, lateral, posterior or inferior. Using the frontal views, the LV lead position was scored as basal, mid or apical. The agreement between the site of latest mechanical activation assessed by 2-dimensional speckle-tracking radial strain analysis and the LV lead position derived from chest X-ray was prospectively analyzed. The LV leads positioned at the latest activated segment were classified as "concordant". In contrast, LV lead positions outside the latest activated segment were classified as "discordant". LV leads located at the apical regions were excluded from further analysis. The inter- and intra-observer agreements for the assessment of LV lead position were excellent (kappa value of 0.88 for both).[13]

Outcome data at long-term follow-up

After CRT implantation, all patients were followed-up at 3-6 monthly intervals until July 2009 at the heart failure outpatient clinic of the CRT implanter center. All-cause mortality, heart transplantation and hospital admission for decompensated heart failure were recorded as events. The primary end-point was the combination of hospitalization for heart failure and all-cause mortality.

Statistical analysis

Continuous variables are expressed as mean±SD, unless otherwise indicated. Categorical data are expressed as frequencies and percentages. Continuous variables were compared

using the Student t-test for unpaired and paired data. Categorical variables were compared with the chi-square test. Cumulative event rates for LV radial dyssynchrony, LV lead position (concordant/discordant) and myocardial scar in the targeted segment were obtained by the Kaplan-Meier method, using all-cause mortality and the combined end point (all-cause mortality and hospitalization for heart failure). Cox proportional hazard analysis was used to determine the value of LV radial dyssynchrony, LV lead position and myocardial scar in the targeted segment to predict long-term survival. First, univariable analysis of baseline clinical and echocardiographic characteristics, LV radial dyssynchrony, LV lead position and myocardial scar in the targeted segment was performed using all-cause mortality as end point. For each variable, the hazard ratio (HR) and the 95% of confidence intervals (CI) were calculated. In the multivariable analysis, the predictive values of LV radial dyssynchrony, LV lead position and myocardial scar in the targeted segment were corrected by those variables with a p-value <0.05 in the univariable analysis. Finally, the relative merits of LV radial dyssynchrony, LV lead position and myocardial scar in the targeted segment over baseline clinical characteristics was assessed by calculating the Harrell's C-concordance statistic and the global chi-square. All statistical analyses were performed with SPSS software (version 15.0, SPSS Inc., Chicago, Illinois) and STATA software (version 10.1, StataCorp, Texas). A p-value <0.05 was considered statistically significant.

RESULTS

Patient population

The baseline characteristics of the 397 patients with chronic, ischemic heart failure (341 [86%] men, mean age 67±10 years) are presented in Table 1. All patients had depressed LV ejection fraction (25±7%), symptomatic advanced heart failure (mean NYHA functional class 3.0±0.3) and a wide QRS complex (155±33 ms). All patients had optimized medical therapy, including angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, beta-blockers and diuretics at maximum tolerated dosages.

Two-dimensional speckle-tracking radial strain analysis

The assessment of LV radial dyssynchrony by 2-dimensional speckle-tracking radial strain analysis was feasible in 389 (98%) patients and mean LV radial dyssynchrony was 133±98 ms (Table 1). Significant LV dyssynchrony (≥130 ms) at baseline was observed in 44% of the patients (Table 1, see also supplemental file).The most frequent site of latest mechanical

Table 1. Baseline characteristics (n = 397)

Clinical variables	
Age (years)	67 ± 10
Gender (male)	341 (86%)
QRS duration (ms)	155 ± 33
Sinus rhythm	321 (81%)
NYHA functional class	3.0 ± 0.3
Quality of life score	36 ± 19
6-minute walking distance (m)	301 ± 115
Medical therapy	
B-blockers	280 (71%)
ACEI/ARB-II	353 (89%)
Diuretics	328 (83%)
Spironolactone	180 (45%)
Statins	304 (77%)
Echocardiographic variables	
LV end-diastolic volume (ml)	216 ± 78
LV end-systolic volume (ml)	161 ± 67
LV ejection fraction (%)	25 ± 7
LV radial dyssynchrony (ms)	133 ± 98
LV radial dyssynchrony ≥130 ms	44%
Discordant LV lead position	32%
Radial strain in the targeted segment (%)	19.1 ± 12.6
Myocardial scar in the targeted segment (radial strain <16.5%) (%)	51

ACEI/ARB-II = angiotensin converting-enzyme inhibitor/angiotensin receptor blockers-II; LV = left ventricular; NYHA = New York Heart Association

activation was the posterior segment (155, 39%), followed by the lateral segment (140, 35%), the inferior segment (28, 7%) and anteroseptal segment (33, 8%).

The LV lead was positioned at the mid-ventricular region in the majority of the patients (351, 88%). This was the posterior region in 178 (45%) patients, the lateral region in 182 (46%) and the anterior region in 37 (9%). In 271 (68%) patients, the LV lead was placed at the latest activated segment as determined by 2-dimensional speckle-tracking radial strain imaging (Table 1). These patients formed the concordant LV lead position group. The remaining 126 (32%) patients, in whom the LV lead position did not coincide with the latest activated segment, formed the discordant LV lead position group (Supplemental file).

Finally, the mean value of peak radial strain was 18.9±12.6% in the segment where the LV lead was positioned. The mean peak radial strain values at the posterior, lateral and anterior segments were 19.3±13.7%, 18.3±12.6% and 15.1±10.1%, respectively. Myocardial scar (defined as strain <16.5%, based on the validation with contrast-enhanced magnetic resonance imaging) in the segment targeted by the LV pacing lead was observed in 51% of the patients (Table 1).

Clinical and echocardiographic follow-up after 6 months of CRT

After 6 months of CRT, a significant improvement in clinical parameters was observed: 259 (65%) patients showed an improvement of at least 1 NYHA functional class, the 6-minute walking distance increased from 306±112 m to 371±121 m ($p<0.001$) and the quality-of-life score improved from 35±19 to 24±19 ($p<0.001$). In addition, there was a significant reduction in LV end-diastolic volume (from 216±78 ml to 181±69 ml, $p<0.001$) and end-systolic volume (from 161±67 ml to 136±58 ml, $p<0.001$), together with a significant improvement in LV ejection fraction (from 25±7% to 31±9%, $p<0.001$). At 6 months follow-up, 231 (58%) patients showed significant LV reverse remodeling, with a reduction in LV end-systolic volume ≥15%. The remaining 166 (42%) did not show significant LV reverse remodeling and were considered non-responders.

LV radial dyssynchrony, LV lead position and myocardial scar in the targeted segment vs. long-term outcome

Long-term follow-up started after CRT implantation. During a median follow-up of 21 months (range 1 – 90), there were 88 hospitalizations for heart failure in 39 (10%) patients and 88 (22%) patients died. During follow-up, none of the patients underwent heart transplantation.

After 3 years of CRT, the survival rate of patients with LV radial dyssynchrony (≥130 ms) was 82% as compared to 65% for patients without substantial dyssynchrony (<130 ms) (log-rank $p<0.001$) (Figure 3, panel A). Similarly, at 3 years follow-up, patients with LV radial dyssynchrony showed a superior survival free rate of combined end point as compared to patients without (75% vs. 63%; log-rank $p = 0.003$) (Figure 3, panel B).

The 3-year survival rate of patients with an LV lead placed at the site of latest mechanical activation (concordant LV lead position) was significantly higher as compared to patients with discordant LV lead position (80% vs. 54%, log-rank $p<0.001$) (Figure 3, panel C). In addition, after 3 years of CRT, the survival free rate of the combined end point was significantly higher in patients with a concordant LV lead position than patients with a discordant LV lead position (75% vs. 54%, log-rank $p<0.001$) (Figure 3, panel D).

Finally, the presence of myocardial scar in the targeted segment had a strong influence on survival free rates (Figure 3, panels E and F). At 3 years follow-up, patients without myocardial scar in the segment where the LV lead was placed (peak radial strain ≥16.5%) showed higher survival rates as compared to patients with myocardial scar in the targeted segment (peak radial strain <16.5%) (87% vs. 58%, log-rank $p<0.001$). Similarly, the 3-year survival free rate of the combined end-point was significantly higher in patients without myocardial scar in the segment targeted by the LV lead as compared to patients with myocardial scar (81% vs. 57%, log-rank $p<0.001$) (Figure 3, panel F).

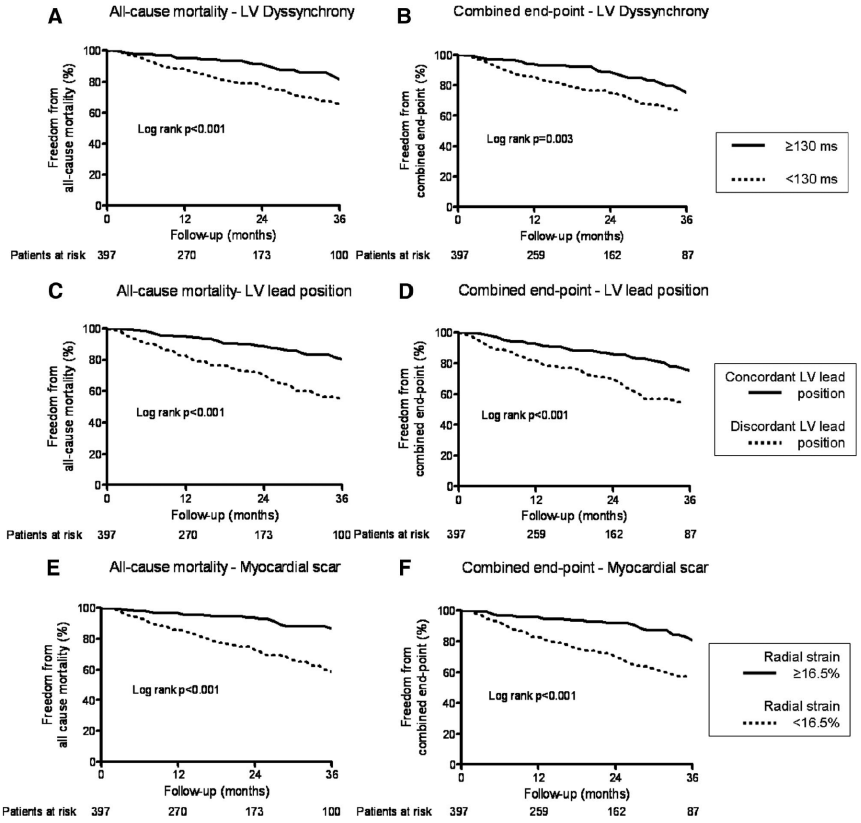

Figure 3. Kaplan-Meier estimates of the time to all-cause mortality and to the combined end-point.
Kaplan-Meier curves for all-cause mortality and the combined end-point are displayed according to presence of substantial LV dyssynchrony (panel A-B), concordant LV lead position (panel C-D) and myocardial scar (panel E-F).

Predictors of long-term survival in ischemic heart failure patients after CRT

The predictive value of LV radial dyssynchrony, LV lead position and myocardial scar in the targeted segment on all-cause mortality was analyzed by Cox proportional hazard analysis. The independent predictors of all-cause mortality were age, plasma levels of creatinine, LV radial dyssynchrony, discordant LV lead position and myocardial scar in the targeted segment (Table 2). In order to evaluate the relative merits of LV radial dyssynchrony, discordant LV lead position and myocardial scar in the targeted segment over the clinical variables to predict long-term outcome, the discrimination indices analysis was performed and the global chi-square scores were calculated. Table 3 shows the Harrell's C-concordance statistic index for each model. The accuracy of the Cox-proportional hazard model to predict long-term outcome progressively increased by adding LV dyssynchrony, discordant LV lead position and

myocardial scar in the segment where the LV lead was positioned. In addition, Figure 4 shows that LV dyssynchrony had an incremental prognostic value over clinical variables (age and creatinine plasma levels). The addition of discordant LV lead position had an incremental prognostic value over the combination of clinical variables and LV dyssynchrony. Finally, the addition of myocardial scar on top of LV radial dyssynchrony and discordant LV lead position resulted in a further improvement of the prognostic stratification of these patients (Figure 4).

Table 2. Cox univariable and multivariable regression analysis to identify predictors of all-cause mortality

	Univariable		**Multivariable**	
	HR (95% CI)	*p-value*	*HR (95% CI)*	*p-value*
Age (per year)	1.028 (1.005-1.052)	**0.017**	1.027 (1.003-1.051)	**0.028**
Male sex	1.060 (0.547-2.052)	0.863	….	…
NYHA functional class	1.953 (1.129-3.376)	0.017	1.447 (0.819-2.558)	0.204
QRS duration (≥150 ms)	1.008 (0.651-1.559)	0.973	…	…
Creatinine (per mmol/mL)	1.003 (1.002-1.004)	**<0.001**	1.004 (1.002-1.007)	**<0.001**
Diabetes mellitus	1.566 (0.982-2.497)	0.060	…	…
LV end-diastolic volume (per ml)	1.001 (0.998-1.004)	0.506	…	…
LV ejection fraction (<25%)	1.568 (1.020-2.409)	**0.040**	1.316 (0.831-2.085)	0.242
LV radial dyssynchrony (per ms)	0.995 (0.992-0.998)	**<0.001**	0.995 (0.992-0.998)	**0.001**
Discordant LV lead position	3.095 (2.033-4.717)	**<0.001**	2.086 (1.336-3.258)	**0.001**
Myocardial scar in the targeted segment (radial strain <16.5%)	3.367 (2.075-5.435)	**<0.001**	2.913 (1.740-4.877)	**<0.001**

CI = confidence interval; HR = hazard ratio; LV = left ventricular; NYHA = New York Heart Association

Table 3. Incremental prognostic value of LV dyssynchrony, discordant LV lead position and myocardial scar: discrimination indices analysis

Model		***Harrell's C-concordance statistic index***
1	Clinical parameters	0.659
2	Clinical parameters + LV dyssynchrony	0.703
3	Clinical parameters + LV dyssynchrony + discordant LV lead position	0.732
4	Clinical parameters + LV dyssynchrony + discordant LV lead position + Myocardial scar	0.751

LV = left ventricular

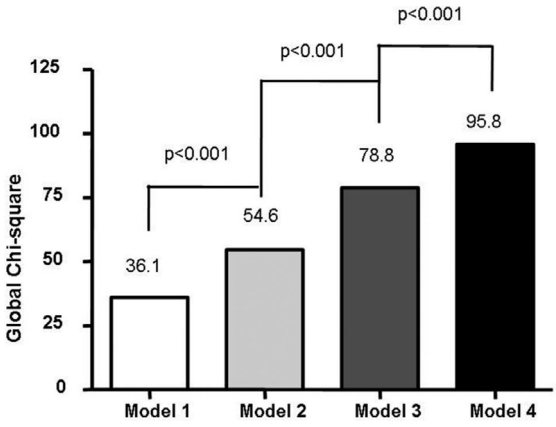

Figure 4. Relative merits of LV radial dyssynchrony, discordant LV lead position and myocardial scar in the targeted segment.
The bar graph shows the χ^2 value for the three models predicting all-cause mortality. The smallest model (model 1) includes clinical variables (age and plasma levels of creatinine) and is nested in model 2, model 3 and model 4. The addition of LV dyssynchrony (model 2) provides incremental prognostic information over baseline clinical variables. Further addition of discordant LV lead position (model 3) provides incremental prognostic information over baseline clinical variables and LV dyssynchrony. Finally, the addition of myocardial scar in the segment targeted by the LV lead (radial strain value <16.5%) (model 4) results in further incremental prognostic value on top of clinical characteristics, LV dyssynchrony and LV lead position.
Model 1 = clinical variables (age, plasma levels of creatinine)
Model 2 = Model 1+ LV dyssynchrony
Model 3 = Model 2 + discordant LV lead position
Model 4 = Model 3 + myocardial scar in the targeted segment

DISCUSSION

The findings of the current study demonstrated that the presence of substantial LV dyssynchrony, appropriate location of the LV pacing lead together with the absence of myocardial scar in the segment targeted by the LV lead were independent determinants of long-term prognosis in ischemic heart failure patients treated with CRT. Furthermore, the combination of these three parameters had an incremental prognostic value over clinical parameters.

Predictors of long-term prognosis after CRT

The benefits of CRT have been mainly evaluated by clinical and echocardiographic criteria: improvement in NYHA functional class, quality-of-life, 6-minute walk distance, LV reverse remodeling, improvement in LV systolic function and mitral regurgitation.[1, 2, 22-26] Various trials have demonstrated the superiority of CRT over optimized medical treatment alone in

improving long-term outcome of advanced heart failure patients.[1, 2] Subsequently, several studies have sought to identify baseline characteristics that predict the effects of CRT on long-term outcome.[7] Thus far, LV dyssynchrony and optimal LV lead position have been shown to predict long-term outcome.[12, 13]

Recent analyses of the CARE-HF trial demonstrated that patients with LV dyssynchrony as measured with the interventricular mechanical delay had a superior long-term outcome than patients without substantial LV dyssynchrony.[27] Similarly, patients with LV dyssynchrony ≥65 ms, as assessed with tissue Doppler imaging, had a superior long-term outcome as compared to patients with LV dyssynchrony <65 ms (6% vs. 50% cumulative event rate, p<0.001).[12] The present study confirmed these results and demonstrated that LV dyssynchrony as quantified with 2-dimensional speckle-tracking radial strain imaging was an independent predictor of long-term outcome of patients with ischemic heart failure. Thus, patients with substantial LV dyssynchrony (≥130 ms) had a superior long-term survival as compared to patients without LV dyssynchrony (82% vs. 65%, p<0.001).

In addition, few studies have demonstrated the value of optimal LV lead position to predict long-term outcome.[13, 28] Recently, in 134 heart failure patients treated with CRT and followed-up for 39±24 months, Zhang et al. demonstrated that the postero-lateral LV lead position predicted lower all-cause and cardiovascular mortality (29% vs. 47%, p = 0.02 and 21% vs. 41%, p = 0.009, respectively).[28] However, positioning the LV pacing lead at the latest activated segment may provide the greatest benefit of CRT as previously demonstrated.[13, 29, 30] Current 2-dimensional speckle-tracking imaging enables to identify the latest activated segments of the LV, indicating the area where the LV lead should be preferably placed. In a series of 244 heart failure patients treated with CRT, the latest activated segment was assessed with 2-dimensional speckle-tracking radial strain imaging and was related to the LV lead position on chest X-ray.[13] Patients with an LV lead placed at the latest activated segment showed superior long-term prognosis in contrast to patients with a discordant LV lead position who had higher event rates at 3 years follow-up (combined for heart failure hospitalizations and all-cause mortality: 43% vs. 22%, p = 0.022).[13] The present study extended these findings, demonstrating the predictive value of an optimal LV lead position and highlighting its incremental predictive value on top of baseline LV dyssynchrony and other clinical variables. However, the present study included patients with LV pacing leads positioned at the basal or mid-ventricular level, and the effect of apical LV lead positions on long-term outcome remain to be established.

In addition, the location and extent of myocardial scar tissue are determinants of CRT response.[9, 10, 31] Patients with transmural scar in the area where the LV lead is placed or patients with large areas of myocardial scar tissue showed a lower response rate to CRT as compared to patients with minimal scar tissue.[9, 10, 31] However, the prognostic predictive value of myocardial scar tissue in ischemic heart failure patients treated with CRT has not been yet established. Delayed contrast-enhanced magnetic resonance imaging and nuclear imaging

are considered "gold standard" to evaluate myocardial scar tissue. Recently, the role of 2-dimensional speckle-tracking radial strain imaging to evaluate myocardial scar tissue has been also demonstrated.[14] In the current study, the presence of myocardial scar in the segment where the LV lead was placed was evaluated with this imaging technique and the results indicated that patients with myocardial scar tissue in the targeted segment (peak radial strain <16.5%) had lower long-term survival rates as compared to patients without myocardial scar (peak radial strain ≥16.5%). More important, the presence of myocardial scar in the segment paced by the LV lead had incremental prognostic value over clinical characteristics, LV reverse remodeling, LV dyssynchrony and optimal LV lead position (χ^2=105.2, p<0.001; see Figure 4).

Therefore, comprehensive assessment of LV dyssynchrony, latest activated segment and myocardial scar tissue appears crucial to select ischemic heart failure patients who will benefit most from CRT. Two-dimensional speckle-tracking radial strain imaging may be of value to assess all these issues before CRT implantation.

Study limitations

The present study included ischemic heart failure patients. Low radial strain can be also observed in patients with non-ischemic heart failure and remodeled left ventricles without myocardial scar.[32] Nevertheless, the cut-off value of radial strain used in the present study was validated with contrast-enhanced magnetic resonance in a sub-group of ischemic heart failure patients. Additional studies including non-ischemic heart failure patients are needed in order to elucidate the role of radial strain speckle-tracking imaging to predict long-term prognosis in these subpopulations.

Clinical implications

Several pathophysiological factors may determine prognosis after CRT. The importance of baseline LV dyssynchrony assessment and optimal LV lead position to predict long-term outcome after CRT have been demonstrated in several studies.[12, 13] However, as indicated previously, positioning the LV pacing lead in a scar segment may limit the improvement in clinical and echocardiographic parameters.[9] The present study extends these results and demonstrates the relative merits of baseline LV dyssynchrony, LV lead position and myocardial scar tissue in the targeted segment. The combination of these three parameters had a strong influence on the long-term outcome of ischemic heart failure patients treated with CRT. Despite substantial LV dyssynchrony or optimal LV lead position at the latest activated segment, the effect of CRT on long-term prognosis may be reduced by the presence of myocardial scar in the region where the LV pacing lead has been placed. In addition, these three

pathophysiological factors had incremental prognostic value over clinical variables. The implementation of an integrated approach that includes assessment of LV dyssynchrony and the latest activated segment together with characterization of myocardial scar may improve patient selection and survival after CRT. Two-dimensional speckle-tracking radial strain imaging may provide this comprehensive evaluation of candidates for CRT.

Conclusions

Long-term outcome of ischemic heart failure patients after CRT implantation is independently determined by baseline LV dyssynchrony, LV lead position and myocardial scar in the region where the LV pacing lead was placed. Larger baseline LV dyssynchrony predicted superior long-term survival whereas discordant LV lead position and myocardial scar predicted worse outcome. These three parameters provided incremental prognostic value over clinical variables. Two-dimensional speckle-tracking radial strain allowed an integrated evaluation of ischemic heart failure patients who are candidates for CRT, by evaluating these three parameters.

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